



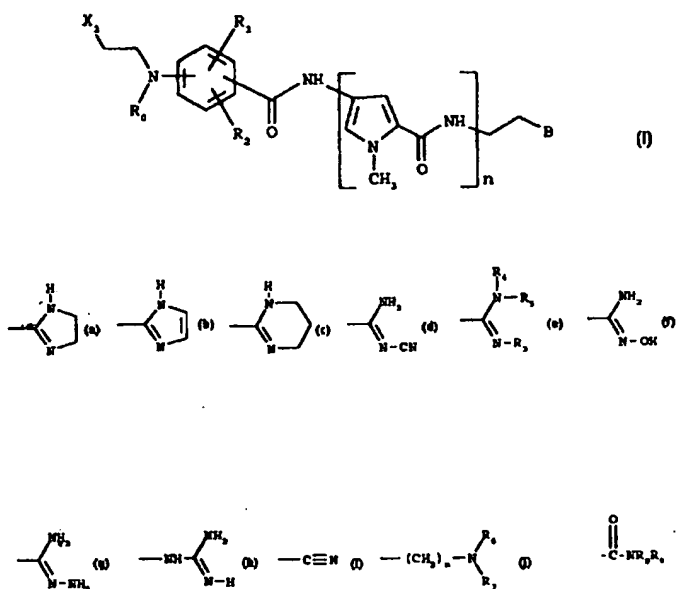
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(54) Title: **DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AND ANTIVIRAL AGENTS**

(57) Abstract

Distamycin derivatives of formula (I) wherein n is 2, 3 or 4; R₀ is C₁-C₄ alkyl or -CH₂CH₂-X₂, wherein X₂ is a halogen atom; R₁ and R₂ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, C₁-C₄ alkoxy, and halogen; X₁ is a halogen atom; B is selected from: (a), (b), (c), (d), (e), (f), (g), (h), (i), (j) and (k); wherein R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are, each independently, hydrogen or C₁-C₄ alkyl, and m is 0, 1 or 2; with the proviso that, when R₀ is -CH₂CH₂-X₂, B is different from -(CH₂)_m-NR₆R₇ and at least one of R₃, R₄, and R₅ is C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof. Such compounds are useful as antineoplastic and antiviral agents.



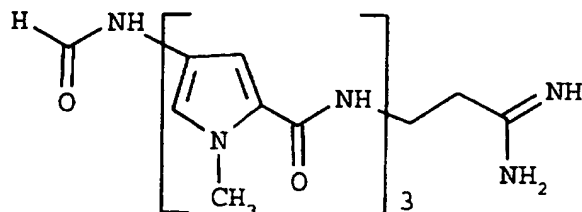
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**DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND
THEIR USE AS ANTITUMOR AND ANTIVIRAL AGENTS**

The present invention refers to new alkylating antitumor and
5 antiviral agents related to the known antibiotic distamycin
A:



which belongs to the family of the pyrroleamidine antibiotics
and is reported to interact reversibly and selectively with
10 DNA-AT sequences interfering with both replication and
transcription [Nature, 203, 1064 (1964); FEBS Letters, 7
(1970) 90; Prog.Nucleic Acids Res.Mol.Biol., 15, 285 (1975)].

DE-A-1795539 describes the preparation of distamycin
15 derivatives in which the formyl group of distamycin is
replaced by hydrogen or by the acid residue of an organic
C₁-C₄ aliphatic acid or of cyclopentylpropionic acid.

EP-B-246,868 describes distamycin analogues in which the
distamycin formyl group is substituted by aromatic, alicyclic
20 or heterocyclic moieties bearing alkylating groups.

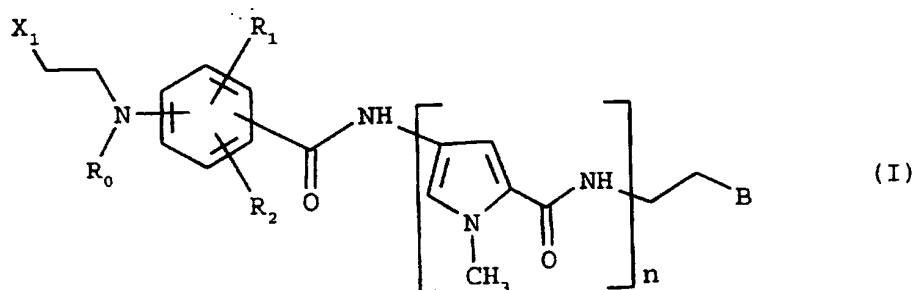
As alkylating groups, N,N-dihaloethylamino moieties, derived
from bifunctional nitrogen mustards, have resulted to be
particularly effective. Conversely, it is well known in the
25 literature that mono-functional nitrogen mustards *per se* (the
so-called half mustards) do not show antitumor activity (see
e.g. T.J. Bardos, J.Med.Chem. 8, 167 (1965) and references
cited therein).

It has now been found that a new class of distamycin derivatives as defined hereinunder, wherein the distamycin formyl group is substituted by a benzoyl moiety bearing as alkylating group a bis-halo-ethylamino moiety (mustard moiety) or a N-alkyl-N-haloethyl-amino group (half mustard moiety), while the amidine group is substituted by various nitrogen-containing end-groups, shows valuable biological properties.

Accordingly, the present invention relates to new distamycin derivatives of formula (I) as defined hereinunder, to a process for preparing them, to pharmaceutical compositions containing them and to their use in therapy, particularly as antitumor and antiviral agents.

15

The present invention provides a distamycin derivative of formula (I):



wherein:

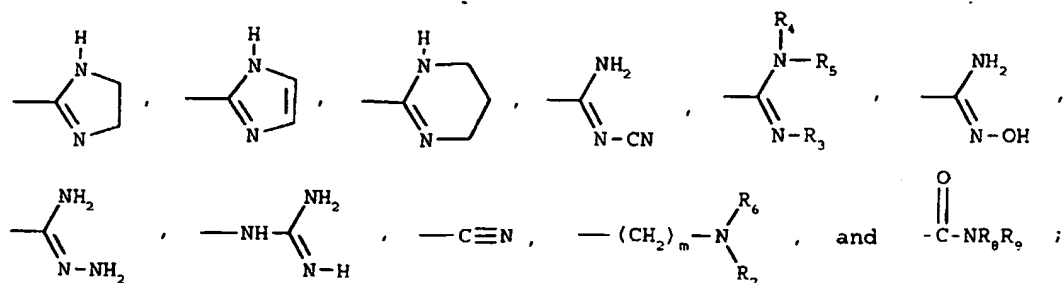
20 n is 2, 3 or 4;

R₀ is C₁-C₄ alkyl or -CH₂CH₂-X₂, wherein X₂ is a halogen atom;

R₁ and R₂ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, C₁-C₄ alkoxy, and halogen;

25 X₁ is a halogen atom;

B is selected from:



wherein R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are, each independently, hydrogen or C_1 - C_4 alkyl, and m is 0, 1 or 2; with the proviso that, when R_0 is $-\text{CH}_2\text{CH}_2-\text{X}_2$, B is different from $-(\text{CH}_2)_m-\text{NR}_6\text{R}_7$ and at least one of R_3 , R_4 , and R_5 is C_1 - C_4 alkyl; or a pharmaceutically acceptable salt thereof.

The present invention includes within its scope also all the possible isomers covered by formula (I) both separately and in mixture, as well as the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

The alkyl and alkoxy groups may have branched or straight chains. A C_1 - C_4 alkyl group is preferably methyl or ethyl, a C_1 - C_4 alkoxy group is preferably methoxy or ethoxy. When substituted by one or more fluorine atoms, a C_1 - C_4 alkyl group is preferably a C_1 - C_4 perfluoroalkyl group, e.g. $-\text{CF}_3$. Halogen is preferably fluorine, chlorine or bromine.

In the phenyl ring, the carboxamide moiety and the half-mustard or the mustard moiety are preferably in meta or para position with respect to each other.

As to the R_1 and R_2 groups, they can be in any of the free positions of the phenyl ring. In a first preferred embodiment R_1 is hydrogen, and R_2 is hydrogen, C_1 - C_4 alkyl optionally

substituted by one or more fluorine atoms, C₁-C₄ alkoxy, or halogen, preferably fluorine; in a second preferred embodiment both R₁ and R₂ are, each independently, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, C₁-C₄ alkoxy, or halogen, preferably fluorine. A particularly preferred value of n is 3; X₁ and X₂ are preferably the same halogen atom, particularly chloro or bromo.

Preferably, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are, each independently, hydrogen, methyl, or ethyl, while R₀ is preferably methyl, ethyl, n-propyl, i-propyl, 2-chloroethyl, or 2-bromoethyl.

Pharmaceutically acceptable salts of the compounds of formula (I) are their salts with pharmaceutically acceptable, either inorganic or organic, acids. Examples of inorganic acids are hydrochloric, hydrobromic, sulfuric and nitric acid; examples of organic acids are acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic and p-toluenesulfonic acid.

A preferred class of compounds according to the present invention is that of formula (I) wherein:

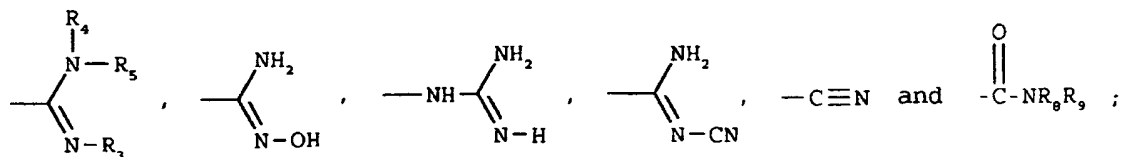
n is 3;

X₁ is chloro or bromo;

R₀ is methyl, ethyl, n-propyl or i-propyl;

R₁ and R₂ are, each independently, hydrogen, -CH₃, -OCH₃, or -CF₃;

B is selected from:



wherein R₃, R₄, R₅, R₈ and R₉ are, each independently,

hydrogen or methyl; or the pharmaceutically acceptable salts thereof.

Another preferred class of compounds according to the present
5 invention is that of formula (I) wherein:

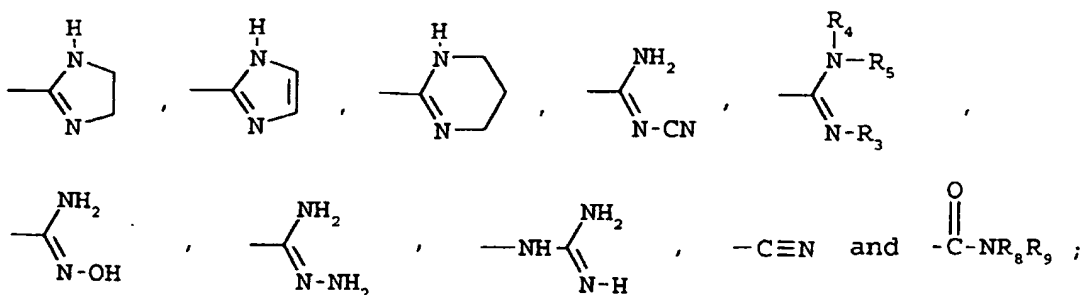
n is 3;

$$R_0 \text{ is } -CH_2CH_2-X_2;$$

X_1 and X_2 are chloro or bromo;

R₁ and R₂ are, each independently, hydrogen, -CH₃, or -OCH₃;

10 B is selected from:



wherein R₃, R₄, R₅, R₈ and R₉ are, each independently, hydrogen or methyl, with the proviso that at least one of R₃,

15 R_4 , and R_5 is methyl;

or the pharmaceutically acceptable salts thereof.

Examples of specific compounds according to the present invention, especially in the form of salts, preferably with hydrochloric or hydrobromic acid, are the following:

- 1) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-methyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 25 2) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propionamidine;
- 3) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 5 4) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 10 5) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 6) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 15 7) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-methoxybenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 20 8) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 25 9) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-trifluoromethylbenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 30 10) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

- propionamidine;
- 11) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 12) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 13) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 14) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 15) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 16) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 17) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propyl-N-methyl-amidine;
- 18) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propion-N-methyl-amidine;
- 19) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 20) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 21) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 22) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 23) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 24) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 25) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 26) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propion-N,N'-dimethyl-amidine;
- 27) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 28) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 29) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 30) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 31) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 32) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 33) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 34) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propionamidoxime;
- 35) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 5 36) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 10 37) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 38) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 15 39) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 20 40) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 25 41) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 30 42) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propioncyanamidine;
- 43) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 44) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 45) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 46) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 47) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 48) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 49) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 50) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- ethylguanidine;
- 51) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 5 52) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline);
- 10 53) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline);
- 54) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)];
- 15 55) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)];
- 20 56) 2-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 25 57) 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 30 58) 2-[1-methyl-4[1-methyl-4[1-methyl-4[3,5-dimethyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- ethyl-1-(2-imidazole);
- 59) 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 60) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 61) 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 62) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 63) 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 64) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 65) 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 66) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

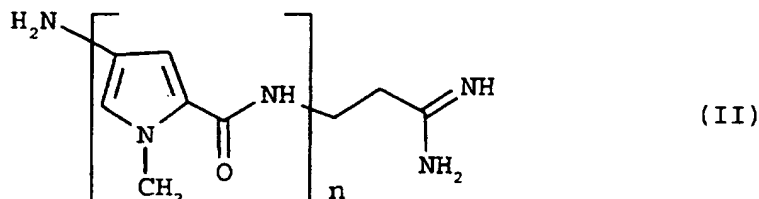
- ethylguanidine;
- 75) 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 5 76) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 10 77) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 15 78) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 20 79) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 25 80) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 30 81) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 82) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propionamide;
- 83) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 5 84) 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amide;
- 10 85) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 86) 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
- 15 87) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amide;
- 20 88) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 25 89) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 30 90) 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

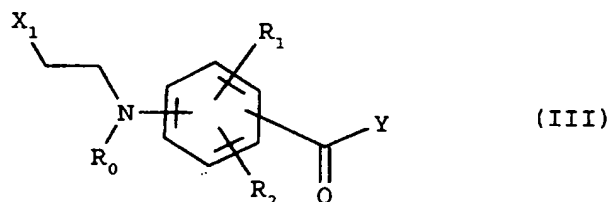
propionitrile.

The present invention also provides a process for the preparation of compounds of formula (I), and the salts thereof, which comprises:

(A) (a) reacting a compound of formula (II):



wherein n is 2, 3 or 4, with a compound of formula (III):



wherein:

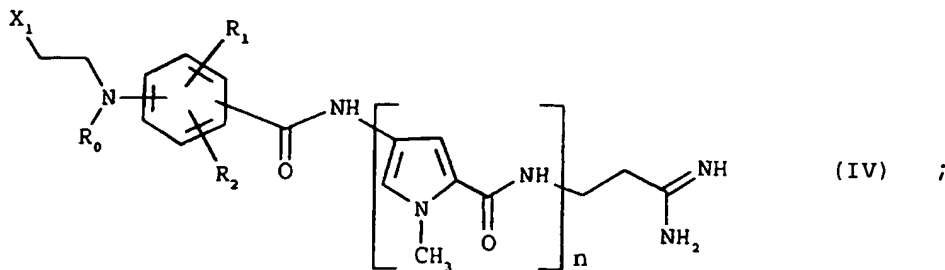
R_0 is C_1 - C_4 alkyl or $-CH_2CH_2-X_2$, wherein X_2 is a halogen atom;

R_1 and R_2 are selected, each independently, from: hydrogen, C_1 - C_4 alkyl optionally substituted by one or more fluorine atoms, C_1 - C_4 alkoxy, and halogen;

X_1 is a halogen atom; and

Y is hydroxy or a leaving group;

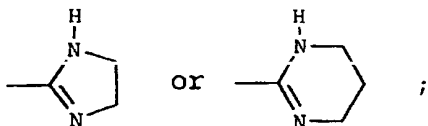
to obtain a compound of formula (IV):



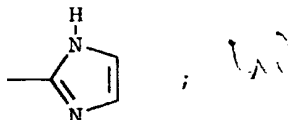
and reacting the compound of formula (IV) with:

(i) $H_2N-(CH_2)_p-NH_2$, where p is 2 or 3, to obtain a

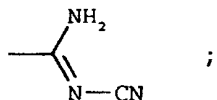
compound of formula (I) wherein B is:



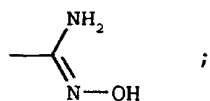
- (ii) $\text{H}_2\text{N}-\text{CH}_2-\text{CHO}$ to obtain a compound of formula (I) wherein B is:



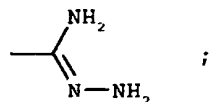
- (iii) $\text{H}_2\text{N}-\text{CN}$ to obtain a compound of formula (I) wherein B is:



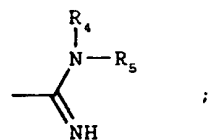
- (iv) $\text{H}_2\text{N}-\text{OH}$ to obtain a compound of formula (I) wherein B is:



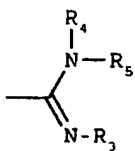
- (v) $\text{H}_2\text{N}-\text{NH}_2$ to obtain a compound of formula (I) wherein B is:



- (vi) HNR_4R_5 to obtain a compound of formula (I) wherein B is:



and if necessary reacting the compound of formula (I) thus obtained with H_2NR_3 , to obtain a compound of formula (I) wherein B is:

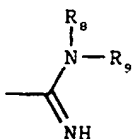


wherein R_3 , R_4 , and R_5 are, each independently, hydrogen or C_1 - C_4 alkyl, with the proviso that at least one of R_3 , R_4 , and R_5 is C_1 - C_4 alkyl;

5 (vii) succinic anhydride to obtain a compound of formula (I) wherein B is $-C\equiv N$;

(viii) water in an alkaline medium, to obtain a compound of formula (I) wherein B is $-CO-NR_8R_9$ with R_8 and R_9 equal to hydrogen; or

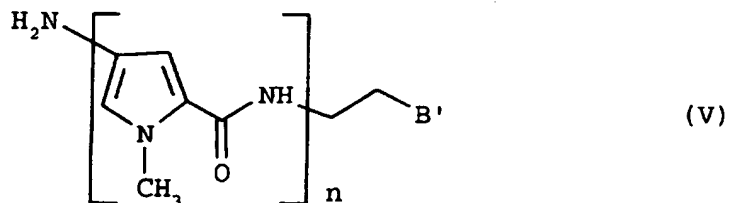
10 (ix) HNR_8R_9 to obtain a compound of formula (I) wherein B is:



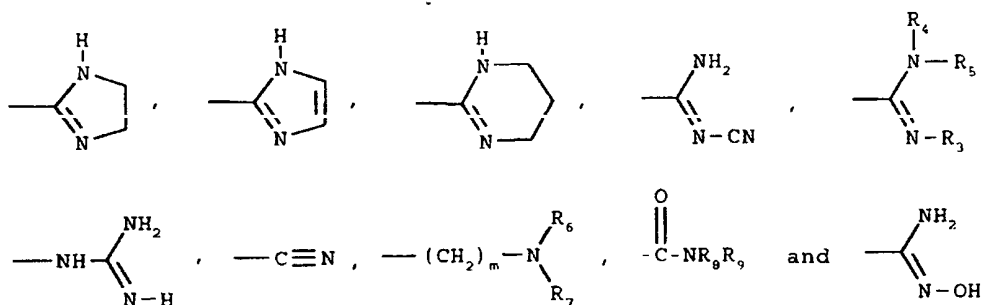
and reacting the compound of formula (I) thus obtained with water in an alkaline medium, to
 15 obtain a compound of formula (I) wherein B is $-CO-NR_8R_9$, with R_8 and R_9 , each independently, equal to hydrogen or C_1 - C_4 alkyl, with the proviso that at least one of R_8 and R_9 is C_1 - C_4 alkyl;

or:

20 (b) reacting a compound of formula (V):

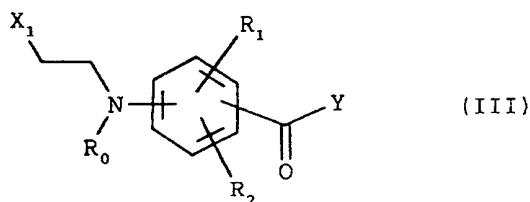


wherein n is 2, 3 or 4; B' is selected from:



wherein R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are each independently hydrogen or C_1 - C_4 alkyl, and m is 0, 1 or 2;

5 with a compound of formula (III):



wherein:

R_0 is C_1 - C_4 alkyl or $-CH_2CH_2-X_2$, wherein X_2 is a halogen atom;

10 R_1 and R_2 are selected, each independently, from: hydrogen, C_1 - C_4 alkyl optionally substituted by one or more fluorine atoms, C_1 - C_4 alkoxy, and halogen;

X_1 is a halogen atom; and

Y is hydroxy or a leaving group;

15 to obtain a compound of formula (I) wherein B is B' as defined above, with the proviso that when R_0 is $-CH_2CH_2-X_2$, B and B' are different from $-(CH_2)_m-NR_6R_7$, and at least one of R_3 , R_4 , and R_5 is C_1 - C_4 alkyl; and

(B) if necessary converting the thus obtained compound of
20 formula (I) into a pharmaceutically acceptable salt thereof.

In formula (III), Y is hydroxy or a leaving group selected, for instance, from chloro, 2,4,5-trichlorophenoxy, 2,4-

dinitro-phenoxy, succinimido-N-oxy, imidazolyl group, and the like.

The reaction of a compound of formula (II) (process (a)) or
5 of formula (V) (process (b)) with a compound of formula (III)
can be carried out according to known methods, for instance
those described in EP-B-246,868.

The reaction between a compound of formula (II) or of formula
(V) and a compound of formula (III) wherein Y is hydroxy, is
10 preferably carried out with a molar ratio (II):(III) or
(V):(III) of from 1:1 to 1:2, in an organic solvent, such as,
e.g., dimethylsulphoxide, hexamethylphosphotriamide,
dimethylacetamide, dimethylformamide, ethanol, benzene, or
pyridine, in the presence of an organic or inorganic base
15 such as, e.g., triethylamine, diisopropyl ethylamine, or
sodium or potassium carbonate or bicarbonate, and of a
condensing agent such as, e.g., N-ethyl-N'-(3-dimethylamino-
propyl)-carbodiimide, N,N'-dicyclohexyl-carbodiimide, and/or
1-hydroxy-benzotriazole hydrate. The reaction temperature
20 may vary from about -10°C to about 100°C, and the reaction
time from about 1 to about 24 hours.

The reaction between a compound of formula (II) or of formula
(V) and a compound of formula (III), wherein Y is a leaving
25 group as defined above, may be carried out with a molar ratio
(II):(III) or (V):(III) of from about 1:1 to about 1:2, in an
organic solvent, such as, e.g., dimethylformamide, dioxane,
pyridine, tetrahydrofurane, or mixtures thereof with water,
optionally in the presence of an organic base, e.g. N,N'-
30 diisopropylethylamine, triethylamine, or an inorganic base,
e.g. sodium or potassium bicarbonate, at a temperature of
from about 0°C to about 100°C, and for a time varying from

about 2 hours to about 48 hours.

The reaction between a compound of formula (IV) and one of the reactants as described at points (i), (ii), (iii), (iv),
5 (v), (vi), or (ix) can be carried out according to known methods, for instance those reported in: US-4,766,142, Chem. Revs. 1961, 155; J. Med. Chem. 1984, 27, 849-857; Chem. Revs. 1970, 151; and "The Chemistry of Amidines and Imidates", edited by S. Patai, John Wiley & Sons, N.Y.
10 (1975).

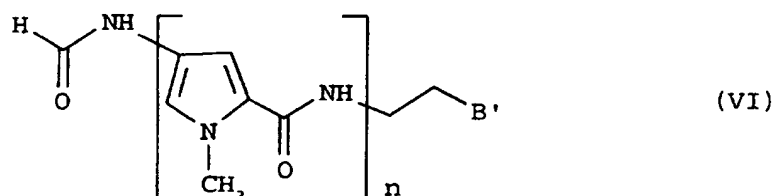
The reaction of a compound of formula (IV) with succinic anhydride (see point (vii) above) is preferably carried out with a molar ratio (IV):succinic anhydride of from 1:1 to 1:3
15 in an organic solvent such as, e.g., dimethyl sulphoxide, dimethylformamide, in the presence of an organic or inorganic base such as, e.g., triethylamine, diisopropylethylamine, sodium or potassium carbonate, and the like. The reaction temperature may vary from about 25°C to about 100°C, and the
20 reaction time from about 1 hour to about 12 hours.

The reaction with water in an alkaline medium (see points (viii) and (ix) above) may be carried out according to known methods usually employed for an alkaline hydrolysis, e.g. by
25 treating the substrate with an excess of sodium or potassium hydroxide dissolved in water or in a mixture of water with an organic solvent, e.g. dioxane, tetrahydrofuran, or acetonitrile, at a temperature of from about 50° to about 100°C, for a time varying from about 2 hours to about 48
30 hours.

The compounds of formula (II) are known compounds or may be prepared by known methods from known compounds: see, for

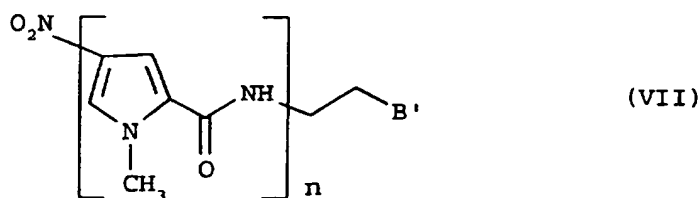
instance, Arcamone et al. *Gazzetta Chim. Ital.* 97, 1097 (1967). The compounds of formula (III) are known compounds too or may be prepared starting from known compounds through reactions well known in organic chemistry: see, for instance, J. Med. Chem. 9, 882 (1966), J. Med. Chem. 25, 178 (1982), J. Org. Chem. 26, 4996 (1961), J. Heterocyclic Chem. 32, 1063 (1995), *Synth. Commun.* 24, 3129-3134 (1994).

The compounds of formula (V) are known compounds, or can be obtained by known methods (see e.g. *Tetrahedron Letters* 31, 1299 (1990), *Anticancer Drug Design* 9, 511 (1994)), such as:
(i) by hydrolytic deformylation, in a basic or acid medium, of compounds of formula (VI):

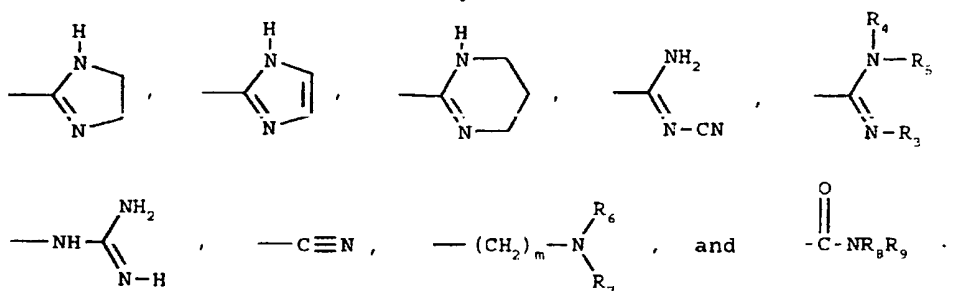


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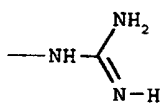
(ii) by nitro-group reduction, according to known methods, of compounds of formula (VII):



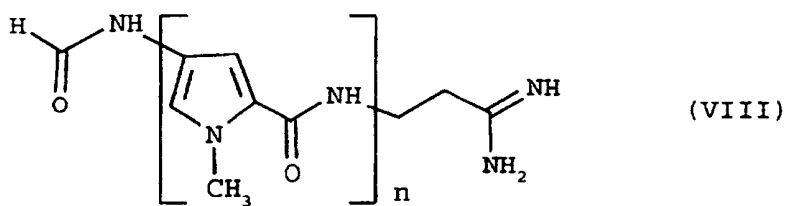
20 wherein B' is selected from:



The compounds of formula (VI), except when B' is equal to



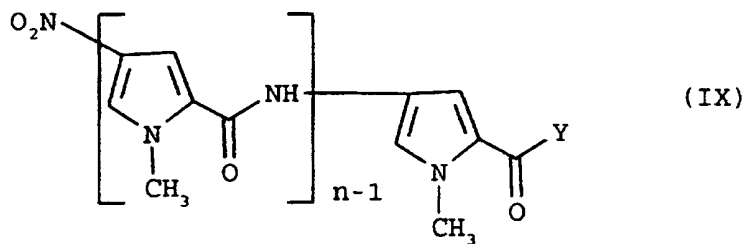
5 can in turn be prepared starting from distamycin compounds of formula (VIII):



using the same reactants as reported in the second step of process (a).

10 The compounds of formula (VII) can be obtained:

(i) from a compound of formula (IX):

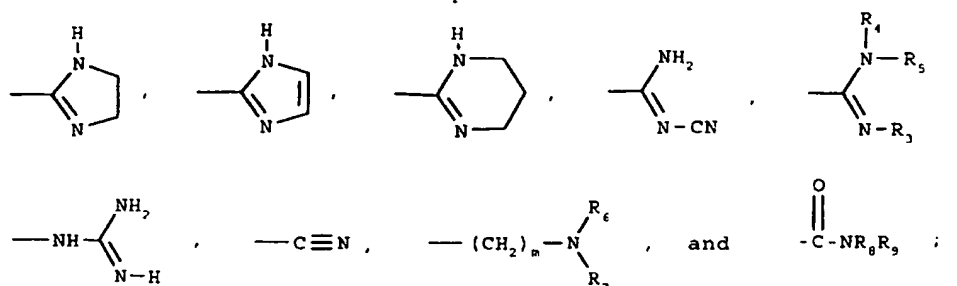


wherein n and Y are as defined above, by reaction with a compound of formula:

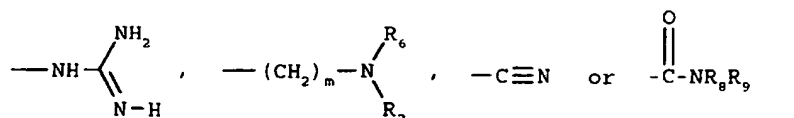


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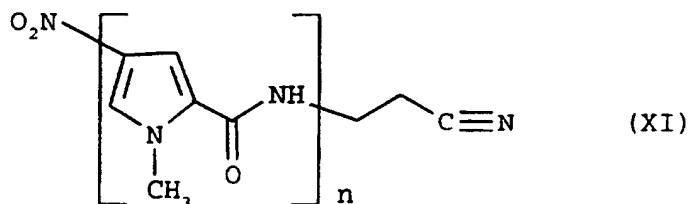
wherein B' is selected from:



(ii) except when B' is equal to



by Pinner reaction of a compound of formula:



5

with a suitable amine compound as defined at point (i), (ii), (iii), or (vi) above.

In the above reaction (i), when at least one of R₆ and R₇ is hydrogen, the amine group may be protected by a suitable protecting group (e.g. benzyl, carbobenzyloxy, and the like).

The compounds of formulas (VIII), (IX), (X) and (XI) are known compounds, or may be obtained by known methods (see e.g. Tetrahedron, 34, 2389-2391, 1978; J. Org. Chem., 46, 3492-3497, 1981).

Salification of a compound of formula (I), as well as preparation of a free compound starting from a salt, may be carried out by known standard methods.

Well known procedures such as, e.g., fractional crystallization or chromatography, may also be followed for separating a mixture of isomers of formula (I) into the

20

single isomers.

The compounds of formula (I) may be purified by conventional techniques such as, e.g., silica gel or alumina column chromatography, and/or by recrystallization from an organic solvent such as, e.g., a lower aliphatic alcohol, e.g. methyl, ethyl or isopropyl alcohol, or dimethylformamide.

PHARMACOLOGY

The compounds of formula (I) or pharmaceutically acceptable salts are useful as antineoplastic and/or antiviral agents. Particularly, they show cytostatic properties towards tumor cells, so that they can be useful to inhibit growth of various tumors in mammals, including humans, such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the present invention can find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g. leukemias.

20

The in vitro antitumor activity was evaluated by cytotoxicity studies carried out on murine L₁₂₁₀ leukemia cells. Cells were derived from in vivo tumors and established in cell culture. Cells were used until the tenth passage. Cytotoxicity was determined by counting surviving cells after 48 hours treatment.

The percentage of cell growth in the treated cultures was compared with that of controls. IC₅₀ values (concentration inhibiting 50% of the cellular growth in respect to controls) were calculated on dose-response.

30

The compounds of the invention were tested also in vivo on

L₁₂₁₀ murine leukemia and on murine reticulosarcoma M 5076 with the following procedure.

L₁₂₁₀ murine leukemia was maintained in vivo by i.v. serial transplantation. For experiments, 10⁵ cells were injected i.p.
5 in CD2F1 female mice, obtained from Charles River Italy. Animals were 8 to 10 weeks old at the beginning of the experiments. Compounds were administered i.v. at day +1 after tumor cells injections.

M5076 reticulosarcoma was maintained in vivo by i.m. serial
10 transplantation. For experiments, 5x10⁵ cells were injected i.m. in C57B16 female mice, obtained from Charles River Italy. Animals were 8 to 10 weeks old at the beginning of the experiments. Compounds were administered i.v. at day 3, 7 and 11 after tumor injection.

15 Survival time of mice and tumor growth were calculated and activity was expressed in term of T/C% and T.I.%.

$$\text{T/C} = \frac{\text{median survival time treated group}}{\text{median survival time untreated group}} \times 100$$

20

T.I. = % inhibition of tumor growth respect to control

Tox: number of mice which died for toxicity.

25 Tox determination was made when mice died before the control and/or tested significant body weight loss and/or spleen and/or liver size reduction were observed.

The compounds of the invention show also a remarkable
30 effectiveness in interfering with the reproductive activity of pathogenic viruses and protect tissue cells from viral infections. For example, they show activity against DNA viruses such as, for instance, herpes, e.g. herpes simplex

and herpes zoster viruses, virus vaccinia, RNA viruses such as, e.g., Rhinovirus and Adenovirus, and against retroviruses such as, for instance, sarcoma viruses, e.g., murine sarcoma virus, and leukemia viruses, e.g. Friend leukemia virus.

5

For example, effectiveness against herpes, coxsackie and respiratory syncytial viruses was tested in a fluid medium as follows. Serial two-fold dilutions of the compounds from 200 to 1.5 mcg/ml were distributed in duplicate 0.1 ml/well in 96 well microplates for tissue culture. Cell suspensions (2×10^5 cells/ml) infected with about 5×10^{-3} TCID₅₀ of virus/cell were immediately added 0.1 ml/well.

After 3-5 day incubation at 37°C in CO₂ 5%, the cell cultures were evaluated by microscope observation and Minimum Inhibiting Concentration (MIC) was determined, MIC being the minimum concentration which determines a reduction of cytopathic effect in comparison with the infected controls.

The compounds of the invention can be administered to mammals, including humans, through the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.1 to about 150-200 mg pro dose 1-4 times a day.

The present invention further provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof as an active principle, in association with one or more pharmaceutically

acceptable carriers and/or diluents.

The pharmaceutical compositions of the present invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as a carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may contain, together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

In the forms for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulation. Said pharmaceutical preparation may be manufactured by known techniques, for

example by means of mixing, granulating, tableting, sugar-coating or film-coating processes.

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in a method of treating the human or animal body by therapy.

Furthermore, the present invention provides a method for treating tumors and viral infections in a patient in need of it, which comprises administering to said patient a composition of the invention.

A further object of the present invention is a combined method for treating cancer or for ameliorating the conditions of mammals, including humans, suffering from cancer, said method comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumor agent, close enough in time and in amounts sufficient to produce a therapeutically useful effect.

The present invention also provides products containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumour agent as a combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

The term "antitumor agent" is meant to comprise both a single antitumor drug and "cocktails" i.e. a mixture of such drugs, according to the clinical practice. Examples of antitumor agents that can be formulated with a compound of formula (I), or alternatively, can be administered in a combined method of treatment, include doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluoro-uracil, melphalan, cyclophosphamide, 4-demethoxy daunorubicin, bleomycin, vinblastin, and mitomycin, or mixtures thereof.

The following examples are given to better illustrate the invention, but do not limit the scope of the invention itself.

5

EXAMPLE 1

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride

Step I The intermediate ethyl N-ethyl-4-aminobenzoate

15 To a solution of 5 g of ethyl 4-aminobenzoate in 100 ml of methanol, 0.74 ml of acetaldehyde, 1.89 g of sodium cyanoborohydride and 2.1 ml of hydrochloric acid 23% were added.

The solution was stirred at room temperature for one day, then the solvent evaporated in vacuo and the crude residue purified by flash chromatography (n-hexane/ethyl acetate 9/1) to yield 2 g of intermediate as a white solid.

EI-MS: m/z 193(80, M⁺); other fragment radicals 178; 150; 148

PMR (CDCl₃) δ:

7.91 (m, 2H), 6.55 (m, 2H), 4.32 (q, J=7.1 Hz, 2H), 4.05 (b.s., 1H), 3.21 (m, 2H), 1.34 (t, J=7.1 Hz, 3H), 1.25 (t, J=7.1 Hz, 3H)

30

By analogous procedure and using the suitable starting materials the following intermediates can be obtained:

ethyl N-methyl-4-aminobenzoate;
ethyl N-propyl-4-aminobenzoate

PMR (CDCl₃) δ :

7.87 (m, 2H), 6.53 (m, 2H), 4.31 (q, J=7.1 Hz, 2H),
5 4.10 (b.s., 1H), 3.16 (t, J=7.2 Hz, 2H), 1.65 (m, 2H),
1.37 (t, J=7.1 Hz, 3H), 1.03 (t, J=7.1 Hz, 3H);

ethyl 3-methyl-N-ethyl-4-aminobenzoate

PMR (CDCl₃) δ :

7.85 (m, 1H), 7.79 (m, 1H), 6.54 (d, J=8.3 Hz, 1H), 4.29
10 (q, J=7.1 Hz, 2H), 3.82 (b.s., 1H), 3.24 (q, J=7.1 Hz,
2H), 2.13 (s, 3H), 1.35 (t, J=7.1 Hz, 3H), 1.30 (t,
J=7.1 Hz, 3H);

ethyl 3,5-dimethyl-N-ethyl-4-aminobenzoate;

ethyl 3-methoxy-N-ethyl-4-aminobenzoate;

15 ethyl 3-methyl-N-ethyl-4-amino-5-methoxybenzoate;

ethyl 3-trifluoromethyl-N-ethyl-4-aminobenzoate; and

ethyl 3-methyl-N-ethyl-4-amino-5-trifluoromethylbenzoate;

Step II The intermediate 4-N-ethyl-N-(2-chloroethyl)
20 aminobenzoic acid

To a solution of 2 g of the intermediate obtained from step I
in 60 ml of methanol, 4 ml of chloroacetaldehyde (40% in
water), 782 mg of sodium cyanoborohydride and 1 ml of
25 hydrochloric acid 23% were added.

The solution was stirred at room temperature for four hours
then the solvent evaporated in vacuo and the crude residue
purified by flash chromatography (n-hexane/ethyl acetate 9/1)
to yield 2 g of ethyl 4-N-ethyl-N-(2-chloroethyl)
30 aminobenzoate as a yellow oil which was dissolved in 20 ml of
37% hydrochloric acid and refluxed for two hours. The mixture
was extracted with ethyl acetate (3 X 100 ml), the combined

organic extracts were washed with water (20 ml), dried on sodium sulfate and concentrated in vacuo to yield 1.8 g of the intermediate as a white solid.

5 EI-MS: m/z 227(20, M⁺); other fragment radicals 178; 150

PMR (CDCl₃) δ:

11.05 (b.s. 1H), 7.96 (m, 2H), 6.65 (m, 2H), 3.64 (m, 4H),
3.51 (q, J=7.1 Hz, 2H), 1.20 (t, J=7.1 Hz, 3H).

10 By analogous procedure and using the suitable starting materials the following products can be obtained:

4-N-methyl-N-(2-chloroethyl)aminobenzoic acid;

4-N-propyl-N-(2-chloroethyl)aminobenzoic acid

PMR (CDCl₃) δ:

15 12.00 (b.s. 1H), 7.94 (m, 2H), 6.66 (m, 2H), 3.18 (m,
4H), 3.34 (t, J=7.2 Hz, 2H), 1.67 (m, 2H), 0.96 (t,
J=7.1 Hz, 3H);

3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzoic acid

PMR (CDCl₃) δ:

20 11.00 (b.s. 1H), 7.93 (m, 1H), 7.89 (m, 1H), 7.10 (d,
J=8.3 Hz, 1H), 3.48 (m, 4H), 3.12 (q, J=7.1 Hz, 2H),
2.36 (s, 3H), 1.08 (t, J=7.1 Hz, 3H);

3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzoic acid;

3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-methoxybenzoic
25 acid;

3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzoic
acid;

3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-
trifluoromethylbenzoic acid;

30 4-N-methyl-N-(2-bromoethyl)aminobenzoic acid; and

3-methyl-4-N-methyl-N-(2-bromoethyl)aminobenzoic acid.

Step III The intermediate 4-N-ethyl-N-(2-chloroethyl)
aminobenzoyl-1-imidazole

5 A solution of 600 mg of the intermediate obtained from step
II and 580 mg of 1,1'-carbonyldiimidazole in 30 ml of ethyl
acetate was stirred at room temperature for three hours. The
solvent was evaporated in vacuo and the crude residue
purified by flash chromatography (ethyl acetate/n-hexane: 7/3)
10 to yield 700 mg of the intermediate as a yellow oil.

EI-MS: m/z 277(10, M⁺); other fragment radicals 228; 210

PMR (CDCl₃) δ:

8.07 (m, 1H), 7.72 (m, 2H), 7.50 (m, 1H), 7.12 (m, 1H), 6.71
15 (m, 2H), 3.69 (m, 4H), 3.51 (q, J=7.1 Hz, 2H), 1.22 (t, J=7.1
Hz, 3H)

By analogous procedure and using the suitable starting
materials the following products can be obtained:

- 20 4-N-methyl-N-(2-chloroethyl)aminobenzoyl-1-imidazole;
4-N-propyl-N-(2-chloroethyl)aminobenzoyl-1-imidazole;
3-methyl-4-N-methyl-N-(2-chloroethyl)aminobenzoyl-1-
imidazole;
3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzoyl-1-
25 imidazole;
3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-methoxybenzoyl-1-
imidazole;
3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzoyl-1-
imidazole;
30 3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-
trifluoromethylbenzoyl-1-imidazole;
4-N-methyl-N-(2-bromoethyl)aminobenzoyl-1-imidazole; and

3-methyl-4-N-methyl-N-(2-bromoethyl)aminobenzoyl-1-imidazole.

Step IV The title compound

5 A solution of 390 mg of the intermediate obtained from step III, 95 mg of imidazole and 738 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride (prepared as reported in J.Med.Chem 32,774-
10 778,1989) in 20 ml of DMF was stirred at room temperature for three hours.

The solvent was evaporated in vacuo and the crude residue purified by flash chromatography (methylene chloride/methanol: 8/2) to yield 400 mg of the title compound as a
15 yellow solid.

FAB-MS: m/z 663 (35, [M+H]⁺); 210

U.V. (EtOH 95%) λ_{\max} =316.8, ϵ =55902

PMR (DMSO-d₆) δ :

20 9.96 (s, 3H), 9.93 (s, 1H), 9.90 (s, 1H), 8.98 (b.s., 2H), 8.65 (b.s., 2H), 8.21 (t, J=5.9 Hz, 1H), 7.82 (m, 2H), 7.27 (d, J=1.7 Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.17 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 6.75 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80
25 (s, 3H), 3.72 (m, 2H), 3.47 (m, 2H), 2.62 (m, 2H), 1.10 (t, J=6.9 Hz, 3H).

By analogous procedure and using the suitable starting materials the following products can be obtained:

30 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-methyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine

hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

5 propionamidine hydrochloride

FAB-MS: m/z 677 (15, [M+H]⁺)

U.V. (EtOH 95%) $\lambda_{\text{max}} = 311.8$, $\epsilon = 44747$.

PMR (DMSO-d₆) δ :

10.19 (s, 1H), 9.99 (s, 1H), 9.93 (s, 1H), 8.98 (b.s.,
2H), 8.63 (b.s., 2H), 8.23 (t, J=5.7 Hz, 1H), 7.80 (m,
1H), 7.76 (m, 1H), 7.31 (d, J=1.8 Hz, 1H), 7.25 (d,
J=1.8 Hz, 1H), 7.21 (d, J=8.3 Hz, 1H), 7.19 (d, J=1.8
Hz, 1H) 7.10 (d, J=1.8 Hz, 1H), 7.07 (d, J=1.8 Hz, 1H),
6.96 (d, J=1.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.81
15 (s, 3H), 3.57 (m, 2H), 3.50 (m, 4H), 3.09 (q, J=7.1 Hz,
2H), 2.62 (t, J=6.5 Hz, 2H), 2.31 (s, 3 H), 0.95 (t,
J=7.1 Hz, 3H);

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
20 propionamidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine
25 hydrobromide;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidine hydrobromide;

30 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine hydrochloride;
- 5 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine hydrochloride;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine; and
- 10 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride.
- 15

EXAMPLE 2

- 20 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride
- 25 A solution of 400 mg of 4-N-propyl-N-(2-chloroethyl)aminobenzoic acid (prepared as reported in example 1 step II) 1 ml of thionyl chloride in 20 ml of benzene was refluxed for two hours, then the solvent was evaporated in vacuo. The crude residue was dissolved in 10 ml dioxane and added in
- 30 small portions to a solution of 200 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine

dihydrochloride (prepared as reported in J.Med.Chem 32,774-778,1989) and 125 mg of potassium bicarbonate in 5 ml of water.

The mixture was stirred at room temperature for one hour, the solvent was evaporated in vacuo and the crude residue purified by flash chromatography (methylene chloride/methanol: 8/2) to yield 140 mg of the title compound.

FAB-MS: m/z 677 (20, [M+H]⁺)

U.V. (EtOH 95%) λ_{\max} = 316.8, ϵ = 56327

PMR (DMSO-d₆) δ :

9.99 (s, 1H), 9.96 (s, 1H), 9.93 (s, 1H), 9.01 (b.s., 2H), 8.69 (b.s., 2H), 8.24 (t, J=5.4 Hz, 1H), 7.83 (m, 2H), 7.30 (d, J=1.6 Hz, 1H), 7.24 (d, J=1.6 Hz, 1H), 7.19 (d, J=1.6 Hz, 1H), 7.08 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.95 (d, J=1.7 Hz, 1H), 6.74 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.73 (m, 6H), 3.37 (m, 2H), 2.62 (t, J=6.5 Hz, 2H), 1.54 (m, 2H), 0.98 (t, J=7.2 Hz, 3H).

By analogous procedure and using the suitable starting materials the following products can be obtained:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine

hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-methoxybenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propionamidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)amino-5-trifluoromethylbenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride; and
5 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride.

10

EXAMPLE 3

- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine hydrochloride
15

- Step I The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine dihydrochloride
20

- A solution of 2 g of distamycin A in 50 ml DMF was treated with 0.38 ml of methylamine hydrochloride 80%. After 8 hours additional 0.25 equivalents of methylamine hydrochloride 80% were added. The solution was evaporated to dryness and the crude residue was purified by flash chromatography (methylene chloride/methanol : 8/2) to give 1.5 g of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine hydrochloride which was dissolved in 40 ml of methanol and added with 5 ml of 2 N hydrochloric
25
30

acid.

The reaction was stirred at room temperature for two days, the solvent evaporated in vacuo and the solid residue suspended in 200 ml of ethyl acetate, yielding after
5 filtration 1.4 g of the intermediate.

FAB-MS: m/z 468 (40, [M+H]⁺)

PMR (DMSO-d₆) δ:

10.20 (s, 3H), 10.18 (s, 1H), 9.98 (s, 1H), 9.65 (m, 1H),
10 9.20 (s, 1H), 8.63 (s, 1H), 8.25 (t, J=5.8 Hz, 1H), 7.25 (d,
J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.11 (d, J=1.7 Hz, 1H)
7.08 (d, J=1.7 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 6.91 (d,
J=1.7 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H),
3.60-3.40 (m, 2H), 2.80 (d, J=6 Hz, 3H), 2.61 (m, 2H).

15

Step II The title compound

A solution of 270 mg of 4-N-ethyl-N-(2-chloroethyl) aminobenzoic acid (prepared as reported in example 1 step
20 II), 1 ml of thionyl chloride in 20 ml of benzene was
refluxed for two hours, then solvent evaporated in vacuo. The
crude residue was dissolved in 10 ml dioxane and added in
small portions to a solution of 200 mg of intermediate
obtained from step I and 248 mg of potassium bicarbonate in
25 10 ml of water.

The mixture was stirred at room temperature for one hour, the
solvent was evaporated in vacuo and the crude residue
purified by flash chromatography (methylene chloride/
methanol: 8/2) to yield 100 mg of the title compound.

30

FAB-MS: m/z 677 (20, [M+H]⁺)

U.V. (EtOH 95%) λ_{\max} = 317, ϵ = 58450

PMR (DMSO-d₆) δ:

9.99 (s, 1H), 9.96 (s, 1H), 9.94 (s, 1H), 9.50 (b.s., 1H),
9.15 (b.s., 1H), 9.60 (b.s., 1H), 8.24 (t, J=5.3 Hz, 1H),
7.83 (m, 2H); 7.30 (d, J=1.6 Hz, 1H), 7.24 (d, J=1.6 Hz, 1H),
5 7.19 (d, J=1.6 Hz, 1H), 7.08 (d, J=1.6 Hz, 1H), 7.06 (d,
J=1.6 Hz, 1H), 6.94 (d, J=1.6 Hz, 1H), 6.75 (m, 2H), 3.85
(s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.71 (m, 4H), 3.60-3.40
(m, 4H), 2.79 (s, 3H), 2.60 (m, 2H), 1.17 (t, J=6.8 Hz, 3H).

10 By analogous procedure and using the suitable starting
materials the following products can be obtained:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
15 amidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-
(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N-methyl-amidine hydrochloride;

20 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-
N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N-methyl-amidine hydrochloride;

25 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-
(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N-methyl-amidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-
ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propyl-N-methyl-amidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-

- bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
amidine hydrobromide;
3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N-
5 (2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N-methyl-amidine hydrobromide;
3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
10 pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N' -
dimethyl-amidine hydrochloride;
3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N' -
15 dimethyl-amidine hydrochloride; and
3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine.

20

EXAMPLE 4

- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
25 pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N' -
dimethyl-amidine hydrochloride

- Step I The intermediate 3- [1-methyl-4- [1-methyl-4- [1-
methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-
30 carboxamido]pyrrole-2-carboxamido]propion-N,N' -
dimethyl-amidine dihydrochloride

A solution of 1.5 g of distamycin A in 40 ml DMF was heated to 80°C and treated with 4 ml of methylamine hydrochloride 80%. After 4 hours additional 5 equivalents (4 ml) of methylamine hydrochloride 80% were added. The solution was
5 evaporated to dryness and the crude residue was purified by flash chromatography (methylene chloride/methanol : 8/2) to yield 1.2 g of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrochloride
10 which was dissolved in 40 ml of methanol and added with 5 ml of 2 N hydrochloric acid solution.

The reaction was stirred at room temperature for two days, the solvent evaporated in vacuo and the solid residue suspended in 200 ml of ethyl acetate, yielding after
15 filtration 1.4 g of the intermediate.

FAB-MS: m/z 482 (45, [M+H]⁺)

PMR (DMSO-d₆) δ:

10.21 (s, 3H), 10.18 (s, 1H), 9.98 (s, 1H), 9.61 (m, 1H),
20 8.85 (s, 1H), 8.39 (t, J=5.8 Hz, 1H), 8.00-7.70 (b.s., 1H),
7.28 (d, J=1.7 Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H) 7.08 (d, J=1.7 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H),
6.92 (d, J=1.7 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H),
3.86 (s, 3H), 3.60-3.40 (m, 2H), 3.02 (d, J=6 Hz, 3H), 2.80
25 (d, J=6 Hz, 3H), 2.72 (m, 2H).

Step II The title compound

A solution of 110 mg of 4-N-ethyl-N-(2-chloroethyl) aminobenzoic acid (prepared as reported in Example 1, step
30 II), 100 mg of dicyclohexylcarbodiimide and 65 mg of 1-hydroxybenzotriazole hydrate in 15 ml of DMF was stirred at 80°C for four hours, cooled to room temperature and then

added with 180 mg of the intermediate obtained from step I and 128 mg of potassium bicarbonate.

The mixture was stirred at room temperature for 3 hours, the solvent was evaporated in vacuo and the crude residue
5 purified by flash chromatography (methylene chloride/methanol: 8/2) to yield 100 mg of the title compound.

FAB-MS: m/z 691 (25, [M+H]⁺)

PMR (DMSO-d₆) δ:

10 9.96 (s, 1H), 9.94 (s, 1H), 9.92 (s, 1H), 9.35 (b.s., 1H),
8.50 (b.s., 1H), 8.26 (t, J=5.6Hz, 1H), 7.42 (m, 2H), 7.27
(d, J=1.6Hz, 1H), 7.21 (d, J=1.6Hz, 1H), 7.17 (d, J=1.6Hz,
1H), 7.05 (d, J=1.6Hz, 1H), 6.95 (d, J=1.6Hz, 1H), 6.92 (d,
J=1.6Hz, 1H), 6.73 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79
15 (s, 3H), 3.72 (m, 4H), 3.55-3.35 (m, 4H), 3.01 (s, 3H), 2.76
(s, 3H), 2.61 (m, 2H), 1.61 (t, J=6.8 Hz, 3H).

By analogous procedure and using the suitable starting material the following products can be obtained:

20 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
25 propion-N,N'-dimethyl-amidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
30 propion-N,N'-dimethyl-amidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-

(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrobromide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrobromide; and
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine.

20

EXAMPLE 5

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine

Step I The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride

30

To a solution of 324 mg of cyanamide in 20 ml of DMF 186 mg of sodium hydride were added. The mixture was stirred at room temperature for 30 min. and then added to a solution of 1 g of distamycin A in 10 ml DMF. The solution was stirred at room temperature for two hours, then acetic acid was added until pH=7. The solvent was removed at reduced pressure and the crude residue purified by flash chromatography (methylene chloride/methanol : 9/1) to give 900 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine which was dissolved in 50 ml of methanol and added with 5 ml of 2 N hydrochloric acid.

The reaction mixture was stirred at room temperature for two days, the solvent was evaporated in vacuo and the solid residue suspended in 200 ml of ethyl acetate, yielding after filtration 600 mg of the intermediate.

FAB-MS: m/z 479 (65, [M+H]⁺)

PMR (DMSO-d₆) δ:

10.11 (s, 3H), 9.97 (s, 1H), 9.80-9.60 (b.s., 2H), 8.50-8.00 (b.s., 3H), 7.40 (t, J=5.8 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 6.88 (d, J=1.7 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.41 (m, 2H), 2.70 (m, 2H).

Step II The title compound

A solution of 180 mg of 4-N-ethyl-N-(2-chloroethyl) aminobenzoic acid (prepared as reported in Example 1, step II) and 1 ml of thionyl chloride in 20 ml of benzene was refluxed for two hours, then the solvent was evaporated in

vacuo. The crude residue was dissolved in 10 ml dioxane and added in small portions to a solution of 110 mg of the intermediate obtained from step I and 40 mg of potassium bicarbonate in 20 ml of water.

- 5 The mixture was stirred at room temperature for one hour, the solvent was evaporated in vacuo and the crude residue purified by flash chromatography (methylene chloride/methanol: 8/2) to yield 90 mg of the title compound.

10 FAB-MS: m/z 688 (15, [M+H]⁺)

PMR (DMSO-d₆ 45°C) δ:

- 9.87 (s, 1H), 9.83 (s, 1H), 9.80 (s, 1H), 8.60-7.90 (b.s., 3H), 7.44 (m, 2H), 7.25 (d, J=1.6 Hz, 1H), 7.22 (d, J=1.6 Hz, 1H), 7.17 (d, J=1.6 Hz, 1H) 7.03 (d, J=1.6 Hz, 1H), 6.92 (d, 15 J=1.6 Hz, 1H), 6.87 (d, J=1.6 Hz, 1H), 6.81 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.50-3.40 (m, 4H), 3.22 (m, 4 H), 2.6 (m, 2H), 1.61 (t, J=6.8 Hz, 3H).

- By analogous procedure and using the suitable starting
20 material the following products can be obtained:

- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 25 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 30 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;

- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
- 5 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
- 10 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N-(2-bromoethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine; and
- 15 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N-(2-bromoethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine.

EXAMPLE 6

- 20 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidoxime

A solution of 165 mg of 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine hydrochloride (prepared as reported in Example 1) in 20 ml DMF was heated to 80°C and treated with 0.48 ml of hydroxylamine 1M in DMF. After 30 min. additional 1 equivalent of hydroxylamine 1M in DMF was added. The solution was evaporated to dryness and the crude residue was purified by flash chromatography (methylene

chloride/methanol: 9/1) to give 90 mg of the title compound as a white solid.

FAB-MS: m/z 679 (20, [M+H]⁺)

5 PMR (DMSO-d₆) δ:

10.02 (s, 1H), 9.96 (s, 1H), 9.91 (s, 1H), 9.40 (b.s., 1H),
8.05 (t, J=5.6 Hz, 1H), 7.45 (m, 2H), 7.29 (d, J=1.7 Hz, 1H),
7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.05 (d,
J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.89 (d, J=1.7 Hz,
10 1H), 6.80 (m, 2H), 6.40-6.20 (b.s., 2H), 3.87 (s, 3H), 3.84
(s, 3H), 3.81 (s, 3H), 3.60-3.50 (m, 4H), 3.24 (m, 4 H), 2.62
(m, 2H), 1.15 (t, J=6.8 Hz, 3H).

By analogous procedure and using the suitable starting
15 materials the following products can be obtained:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-
20 (2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidoxime;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-
N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
25 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidoxime;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-
(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
30 propionamidoxime;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-
ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-

- carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidoxime;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-
bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
5 pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-
(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidoxime;
10 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
amidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-
15 ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N,N'-dimethyl-amidine hydrochloride; and
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-
N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-
20 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine.

EXAMPLE 7

- 25 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine
hydrochloride

- 30 Step I The intermediate 2-aminoethylguanidine
dihydrochloride

A solution of commercial N-BOC-ethylendiamine (1 g) in dry ethanol (100 ml) and 2-methyl-2-thiopseudourea hydroiodide (1.5 g) was refluxed for 8 hours. The solvent was removed at reduced pressure and the crude residue purified by flash chromatography (methylene chloride/methanol : 9/1) to yield 1.5 g of N-BOC-2-aminoethylguanidine hydroiodide as a yellow oil which was dissolved in methanolic hydrochloric acid solution 5N (20 ml) and stirred at room temperature for 3 hours. The white precipitate was collected, washed with dry ethanol, affording 700 mg of the intermediate.

FAB-MS: m/z 103 (20, [M+H]⁺)

PMR (DMSO-d₆) δ :

8.38 (b.s., 3H), 7.97 (t, J= 6 Hz, 1H), 7.51 (b.s., 4H), 3.45 (m, 2H), 2.92 (m, 2H).

Step II The intermediate 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine dihydrochloride

A solution of 1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxylic acid (590 mg) (prepared as reported in Tetrahedron 34,2389-2391,1978) in 20 ml of DMF, 2-aminoethylguanidine dihydrochloride (500 mg), 1-hydroxybenzotriazole hydrate (350 mg), dicyclohexylcarbodiimide (880 mg), and sodium bicarbonate (385 mg) was stirred at 70°C for 4 hours. The solution obtained after filtration was evaporated in vacuo and the residue purified by flash chromatography (methylene chloride/methanol: 8/2) to yield 800 mg of 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride, which was dissolved in methanol (100 ml), added with 1N hydrochloric acid solution (2 ml) and reduced over Pd catalyst (10% on charcoal) in hydrogen atmosphere (50 psi) in a Parr apparatus. The solution obtained after filtration of the catalyst was evaporated in vacuo and the solid residue washed with dry ethanol to yield 750 mg of the intermediate as a brown powder.

10 FAB-MS: m/z 469 (15, [M+H]⁺)

PMR (DMSO-d₆)δ:

10.38-10.11 (b.s., 4H), 9.98 (s, 1H), 8.28 (b.s., 1H), 8.19 (d, J= 1.7 Hz, 1H), 7.73, (b.s., 1H), 7.63 (d, J= 1.7 Hz, 1H), 7.60-7.00 (b.s., 4H), 7.28 (d, J= 1.7 Hz, 1H), 7.20 (d, J= 1.7 Hz, 1H), 7.1 (d, J= 1.7 Hz, 1H), 6.92 (d, J= 1.7 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.28 (m, 4H).

By analogous procedure and using the suitable starting materials the following products can be obtained:

20 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

25 propion-N-methyl-amidine dihydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

propion-N,N'-dimethyl-amidine dihydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-

30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

ethyl-1-(2-imidazole) hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] dihydrochloride;
2-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
5 ethyl-1-(2-imidazoline) dihydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamide hydrochloride; and
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-
10 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionitrile hydrochloride.

Step III The title compound

15 A solution of 600 mg of 4-N-ethyl-N-(2-chloroethyl)
aminobenzoic acid (prepared as reported in example 1 step II)
3 ml of thionyl chloride in 60 ml of benzene was refluxed for
two hours, then the solvent was evaporated in vacuo. The
crude residue was dissolved in 50 ml dioxane and added in
20 small portions to a solution of 250 mg of the intermediate
and 125 mg of potassium bicarbonate in 10 ml of water.
The mixture was stirred at room temperature for one hour, the
solvent was evaporated under vacuo and the crude residue
purified by flash chromatography (methylene chloride/
25 methanol: 8/2) to yield 50 mg of the title compound as a
yellow solid.

FAB-MS: m/z 678 (15, [M+H]⁺); 210

PMR (DMSO-d₆) δ:

30 9.94 (s, 1H), 9.92 (s, 1H), 9.90 (s, 1H), 8.09 (b.s., 1H),
7.81 (m, 2H), 7.52 (b.s., 1H), 7.2 (b.s., 4H), 7.27 (d, J=1.7
Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.17 (d, J=1.7 Hz, 1H), 7.07

(d, J=1.7 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 6.95 (d, J=1.7 Hz, 1H), 6.75 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.72 (m, 4H), 3.47 (m, 2H), 3.30 (m, 4H), 1.10 (t, J=6.9 Hz, 3H).

5

By analogous procedure and using the suitable starting materials the following products can be obtained:

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride; and

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-

- (2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] ethylguanidine hydrochloride;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

propionamide;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
5 amide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide; and
10 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amide.

15

EXAMPLE 8

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime
20

Step I The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime
25 hydrochloride

1.2 g of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile (prepared as reported in J. Med. Chem 22, 1296-
30 1301, 1979) was suspended in dry ethanol and the solution saturated with dry hydrogen chloride. After 24 hours at room temperature, the solvent was evaporated under vacuo and the

residue treated with two equivalents of solution of hydroxylamine in dry ethanol. After 24 hours at room temperature, the solvent was evaporated in vacuo and the residue purified by flash chromatography yielding 500 mg of
5 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime which was dissolved in a mixture of methanol-dioxane-10% hydrochloric acid (4:1:1) and reduced over Pd catalyst (10% on charcoal) in hydrogen atmosphere (50
10 psi) in a Parr apparatus.

The solution obtained after filtration of the catalyst was evaporated in vacuo, and the solid residue suspended in dry ethanol, and filtered to yield 500 mg of the intermediate.

15 FAB-MS: m/z 480 (20, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.18 (b.s., 6H), 9.98 (s, 1H), 8.32 (t, J=5.7 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.20 (d, J=1.7 Hz, 1H), 7.16 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.10 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (b.s., 7H),
20 3.50 (m, 2H), 2.72 (m, 2H).

By analogous procedure and using the suitable starting materials the following products can be obtained:

25 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
30 propion-N-methyl-amidine dihydrochloride; and
2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

propion-N,N'-dimethyl-amidine dihydrochloride.

Step II The title compound

5 A solution of 160 mg of 4-N-ethyl-N-(2-chloroethyl) aminobenzoic acid (prepared as reported in example 1 step II) and 106 mg of 1-hydroxybenzotriazole hydrate in 10 ml of DMF was stirred at 70°C for four hours, cooled to room temperature and then added with 310 mg of the intermediate
10 obtained from step I and 118 mg of potassium bicarbonate in 20 ml of water.

The mixture was stirred at room temperature for 3 hours, the solvent was evaporated in vacuo and the crude residue purified by flash chromatography (methylene chloride/
15 methanol: 8/2) to yield 180 mg of the title compound as a yellow solid.

FAB-MS: m/z 679 (20, [M+H]⁺)

PMR (DMSO-d₆) δ:

20 10.02 (s, 1H), 9.96 (s, 1H), 9.91 (s, 1H), 9.40 (b.s., 1H),
8.05 (t, J=5.6 Hz, 1H), 7.45 (m, 2H), 7.29 (d, J=1.7 Hz, 1H),
7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.05 (d,
J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.89 (d, J=1.7 Hz,
1H), 6.80 (m, 2H), 6.40-6.20 (b.s., 2H), 3.87 (s, 3H), 3.84
25 (s, 3H), 3.81 (s, 3H), 3.60-3.50 (m, 4H), 3.24 (m, 4 H), 2.62
(m, 2H), 1.15 (t, J=6.8 Hz, 3H).

By analogous procedure and using the suitable starting materials the following products can be obtained:

30 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;

- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidoxime;
- 5 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidoxime;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propion-N-methyl-amidine hydrochloride;
- 10 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propion-N-methyl-amidine hydrochloride;
- 15 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propion-N-methyl-amidine hydrochloride;
- 20 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propion-N,N'-dimethyl-amidine hydrochloride;
- 25 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propion-N,N'-dimethyl-amidine hydrochloride;
- 30 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propion-N,N'-dimethyl-amidine hydrochloride;

- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
- 5 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
- 10 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
- 15 2- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethylguanidine hydrochloride;
- 20 2- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethylguanidine hydrochloride;
- 25 2- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethylguanidine; and
- 2- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethylguanidine hydrochloride.

EXAMPLE 9

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline) hydrochloride.

A solution of 300 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide hydrochloride (prepared as reported in J.Med.Chem. 32,774-778, 1989) in 50 ml of acetonitrile and 20 ml of water was treated with ethylendiamine (0.2 ml). The resulting solution was kept at room temperature for 24 hours and the whole evaporated in vacuo. The residue was purified by flash chromatography (methylene chloride/methanol : 8/2) to give 80 mg of the title compound as a yellow solid.

FAB-MS: m/z 697, (15, [M+H]⁺); 244, (18)

PMR (DMSO-d₆) δ :

10.00 (b.s., 2H), 10.03 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H), 8.29 (t, J=5.7Hz, 1H), 7.84 (m, 2H), 7.29 (d, J=1.8Hz, 1H), 7.23 (d, J=1.8Hz, 1H), 7.19 (d, J=1.8Hz, 1H), 7.07 (d, J=1.8Hz, 1H), 7.06 (d, J=1.8Hz, 1H), 6.93 (d, J=1.8Hz, 1H), 6.82 (m, 2H), 3.90-3.60 (m, 12H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 2.68 (t, J=6.7Hz, 2H)

By analogous procedure and using the opportune starting materials the following compounds can be obtained:

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride

5 FAB-MS: m/z 711, (20, [M+H]⁺); 244, (40)

PMR (DMSO-d₆) δ :

10.15 (s, 1H), 9.90 (s, 2H), 8.25 (t, J=5.7Hz, 1H), 7.82 (m, 2H), 7.27 (d, J=1.8Hz, 1H), 7.23 (d, J=1.8Hz, 1H), 7.20 (d, J=1.8Hz, 1H), 7.05 (d, J=1.8Hz, 1H) 7.03 (d, J=1.8Hz, 1H), 6.92 (d, J=1.8Hz, 1H), 7.30-6.92 (m, 6H), 6.84 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73-3.63 (m, 8H), 3.52-3.00 (m, 6H), 2.60 (t, J=6.7Hz, 2H), 1.75 (m, 2H);

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline) hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride;

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline) hydrochloride;

25 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride.

EXAMPLE 10

30

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole).

A solution of 200 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide hydrochloride (prepared as reported in J. Med. Chem. 32, 774-778, 1989) in 10 ml of DMF was treated with 90 μ l of aminoacetaldehyde dimethylacetale and heated at 70°C for 4 hours. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (methylene chloride/methanol : 9/1) to give 40 mg of the title compound as a yellow solid.

FAB-MS: m/z 721, (8, [M+H]⁺); 244, (100)

15

PMR(DMSO-d₆) δ :

10.01 (s, 1H), 9.94 (s, 1H), 9.90 (s, 1H), 8.12 (t, J=5.8Hz, 1H), 7.84 (m, 2H), 7.30 (d, J=1.8Hz, 1H), 7.24 (d, J=1.8Hz, 1H), 7.20 (d, J=1.8Hz, 1H) 7.06 (d, J=1.8Hz, 1H), 7.04 (d, J=1.8Hz, 1H), 6.83 (d, J=1.8Hz, 1H), 6.87 (s, 2H), 6.82 (m, 2H), 3.42 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.48 (m, 3H), 2.81 (m, 2H)

By analogous procedure and using the opportune starting materials the following products can be obtained:

2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);

2-[1-methyl-4[1-methyl-4[1-methyl-4[3,5-dimethyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]

pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
5 pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
2-[1-methyl-4[1-methyl-4[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
ethyl-1-(2-imidazole).

10

EXAMPLE 11

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
15 carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine hydrochloride.

A solution of 200 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-
20 2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride (prepared as reported in J. Med. Chem. 32, 774-778, 1989) in 5 ml DMF was treated with 0.023 ml of methylamine hydrochloride 80%. After 4h additional 0.5 equivalent of methylamine hydrochloride 80% was added. The
25 solution was evaporated to dryness and the crude residue was purified by flash chromatography (methylene chloride/methanol : 9/1) to give 100 mg of the title compound as a white solid.

30 FAB-MS: m/z 710, (20, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.07 (s, 1H), 9.98 (s, 1H), 9.95 (s, 1H), 9.65-9.45 (b.s., 1H), 9.25-9.05 (b.s., 1H), 8.70-8.50 (b.s., 1H), 8.26 (t, J=5.8Hz, 1H), 7.86 (m, 2H), 7.31 (d, J=1.7Hz, 1H), 7.25 (d, J=1.7Hz, 1H), 7.20 (d, J=1.7Hz, 1H), 7.10 (d, J=1.7Hz, 1H),
5 7.07 (d, J=1.7Hz, 1H), 6.93 (d, J=1.7Hz, 1H), 6.82 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.75-3.55 (m, 8H), 3.45 (m, 2H), 2.79 (s, 3H), 2.55 (m, 2H)

By analogous procedure and using the opportune starting
10 material the following product can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
15 amidine hydrochloride..

EXAMPLE 12

3[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
20 aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine hydrochloride.

A solution of 200 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride (prepared as reported in J. Med. Chem. 32, 774-778, 1989) in 5 ml DMF was heated at 70°C and treated with 0.115 ml of methylamine hydrochloride 80%. After
25 30 4h additional 5 equivalent of methylamine hydrochloride 80% was added. The solution was evaporated to dryness and the crude residue was purified by flash chromatography

(methylene chloride/methanol : 9/1) to give 120 mg of the title compound as a white solid.

FAB-MS: m/z, 724 (25, [M+H]⁺)

5

PMR (DMSO-d₆) δ :

10.07 (s, 1H), 9.98 (s, 1H), 9.96 (s, 1H), 9.60-9.40 (b.s., 1H), 8.85-8.65 (b.s., 1H), 8.34 (t, J=5.2Hz, 1H), 7.85 (m, 2H), 7.30 (d, J=1.5Hz, 1H), 7.24 (d, J=1.5Hz, 1H), 7.20 (d, J=1.5Hz, 1H) 7.07 (m, 2H), 6.93 (d, J=1.5Hz, 1H), 6.82 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.75-3.55 (m, 8H), 3.40 (m, 2H), 3.00 (s, 3H), 2.78 (s, 3H), 2.60 (m, 2H)

By analogous procedure and using the opportune starting material the following product can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine hydrochloride.

EXAMPLE 13

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime.

A solution of 500 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride (prepared as reported in J. Med. Chem. 32, 774-778, 1989) in 20 ml DMF was heated at 60°C and

treated with 0.68 ml of hydroxylamine 1M in DMF obtained from hydroxylamine hydrochloride (70 mg), 0.139 ml triethylamine and 1 ml DMF with 10% water. After 30' additional 1 equivalent of hydroxylamine 1M in DMF was added. The solution
5 was evaporated to dryness and the crude residue was purified by flash chromatography (methylene chloride/methanol : 85/15) to give 400 mg of the title compound as a white solid.

FAB-MS: m/z 713, (70, [M+H]⁺); 244, (40)

10

U.V. (MeOH) λ_{\max} 312.85 , ϵ = 56445

PMR (DMSO-d₆) δ :

9.98 (s, 1H), 9.92 (s, 1H), 9.86 (s, 1H), 8.82 (s, 1H), 7.87
15 (t, J=5.7Hz, 1H), 7.83 (m, 2H), 7.28 (d, J=1.7Hz, 1H), 7.23
(d, J=1.7Hz, 1H), 7.17(d, J=1.7Hz, 1H) 7.06 (d, J=1.7Hz, 1H), 7.04 (d, J=1.7Hz, 1H), 6.83 (d, J=1.7Hz, 1H), 6.82 (m, 2H), 5.40 (b.s., 2H), 3.90-3.70 (m, 8H), 3.85 (s, 3H), 3.83(s, 3H), 3.79 (s, 3H), 3.32 (m, 2H), 2.20 (m, 2H)

20

By analogous procedure and using the opportune starting material the following product can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
25 chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-bromoethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido] propionamidoxime.

EXAMPLE 14

3 [1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
5 carboxamido]pyrrole-2-carboxamido]propioncyanamidine.

To a solution of 50 mg of cyanamide in 5 ml of DMF were added
30 mg of sodium hydride. The mixture was stirred at room
temperature for 15' and then added to a solution of 200 mg of
10 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
hydrochloride (prepared as reported in J. Med. Chem. 32, 774-
778, 1989) in 5 ml DMF. The solution was stirred at room
15 temperature for 30', then acetic acid was added until pH=7.
The solvent removed under reduced pressure and the crude
residue was purified by flash chromatography (methylene
chloride/methanol : 9/1) to give 90 mg of the title compound
as a white solid.

20

FAB-MS: m/z 722, (10, [M+H]⁺); 366, (10); 244, (80)

PMR (DMSO-d₆, 75°C) δ :

9.76 (s, 1H), 9.68 (s, 1H), 9.65 (s, 1H), 8.10 (b.s., 1H),
25 8.00 (b.s., 1H), 7.84 (m, 3H), 7.24 (d, J=1.8Hz, 1H), 7.19
(d, J=1.8Hz, 1H), 7.15 (d, J=1.8Hz, 1H), 7.05 (d, J=1.8Hz,
1H), 7.03 (d, J=1.8Hz, 1H), 6.87 (d, J=1.8Hz, 1H), 6.83 (m,
2H), 3.90-3.70 (m, 8H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s,
3H), 3.48 (m, 2H), 2.61 (m, 2H)

30

By analogous procedure and using the opportune starting
materials the following products can be obtained:

- 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
- 5 propioncyanamidine;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4[3,5-dimethyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
- propioncyanamidine;
- 10 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
- propioncyanamidine;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4-formamidopyrrole-2-
- 15 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
- propioncyanamidine.

EXAMPLE 15

- 20 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidrazone.

A solution of 250 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride (prepared as reported in J. Med. Chem. 32, 774-778, 1989) in 8 ml DMF and 0.04 ml of hydrazine hydrate was stirred for 15' at 25°C then 2N hydrochloric acid

30 was added until pH=5, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (methylene chloride/methanol : 9/1) to give 100 mg of the title compound

as a yellow solid.

FAB-MS: m/z 712, [18, (M+H)⁺]

5 PMR (DMSO-d₆) δ :

10.05 (s, 1H), 9.93 (s, 1H), 9.90 (s, 1H), 8.70 (b.s., 2H),
8.19 (t, J=5.70Hz, 1H), 7.83 (m, 2H), 7.27 (d, J=1.8Hz, 1H),
7.21 (d, J=1.8Hz, 1H), 7.16 (d, J=1.8Hz, 1H), 7.06 (d,
J=1.8Hz, 1H), 7.03 (d, J=1.8Hz, 1H), 6.91 (d, J=1.8Hz, 1H),
10 6.78 (m, 2H), 5.00 (b.s., 2H), 3.90-3.60 (m, 8H), 3.81 (s,
3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.44 (m, 2H), 2.57 (t,
J=6.5Hz, 2H)

By analogous procedure and using the opportune starting
15 material the following product can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]
20 propionamidrazone.

EXAMPLE 16

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
25 aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionitrile.

To a solution of 1.30 g of 3-[1-methyl-4[1-methyl-4[1-
methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]
30 pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride (prepared as
reported in J. Med. Chem. 32, 774-778, 1989) in 20 ml DMF

were added 535 mg of potassium carbonate and 385 mg of succinic anhydride. The mixture was heated at 60°C for 4 hours. The solvent evaporated under vacuum and the crude residue purified by flash chromatography (methylene chloride/methanol : 8/2) to yield 600 mg of the title compound as a yellow powder.

FAB-MS: m/z 680, (8, [M+H]⁺); 488, (10); 366, (15); 244, (100)

10

PMR (DMSO-d₆) δ :

10.01 (s, 1H), 9.96 (s, 1H), 9.94 (s, 1H), 8.34 (t, J=6.0Hz, 1H), 7.84 (m, 2H), 7.30 (d, J=1.8Hz, 1H), 7.25 (d, J=1.8Hz, 1H), 7.22 (d, J=1.8Hz, 1H), 7.07 (d, J=1.8Hz, 1H), 7.05 (d, J=1.8Hz, 1H), 6.94 (d, J=1.8Hz, 1H), 6.83 (m, 2H), 3.90-3.60 (m, 8H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.40 (m, 2H), 2.72 (t, J=6.4Hz, 2H)

By analogous procedure and using the opportune starting materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile;
3-[1-methyl-4[1-methyl-4[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile.

EXAMPLE 17

30

2-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

**carboxamidolpyrrole-2-carboxamidol ethylguanidine
hydrochloride.**

A solution of 4-[N,N-bis(2-chloroethyl)amino]benzoyl chloride
5 (590 mg) (prepared as reported in J. Med. Chem. 32, 774-778,
1989) in 20 ml of dioxane was added slowly to a solution of
the intermediate obtained in Example 7, step II, above (500
mg) in 20 ml of water containing sodium bicarbonate (237 mg).
The mixture was stirred at room temperature for 3 hours, the
10 aqueous solution was evaporated in vacuo to dryness and the
solid residue purified by flash chromatography (methylene
chloride/ methanol: 8/2) to yield 450 mg of the title
compound as a yellow powder.

15 FAB-MS: m/z 712, (20, [M+H]⁺); 244, (100)

U.V. (EtOH 95%) λ_{\max} = 312.8, ϵ = 54227

PMR (DMSO-d₆) δ :

20 10.02 (s, 1H), 9.93 (s, 1H), 9.91 (s, 1H), 8.85 (m, 2H), 8.12
(b.s., 1H), 7.65 (b.s., 1H), 7.20 (b.s., 4H), 7.29 (d,
J=1.8Hz, 1H), 7.23 (d, J=1.8Hz, 1H), 7.19 (d, J=1.8Hz, 1H),
7.08 (d, J=1.8Hz, 1H), 7.06 (d, J=1.8Hz, 1H), 6.94 (d,
J=1.8Hz, 1H), 6.82 (m, 2H), 3.90-3.70 (m, 8H), 3.85 (s, 3H),
25 3.84 (s, 3H), 3.81 (s, 3H), 3.40-3.10 (m, 4H)

By analogous procedure and using the opportune starting
materials the following products can be obtained:

30 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine

- hydrochloride;
2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 5 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 10 2-[1-methyl-4[1-methyl-4[1-methyl-4[3,6-dimethyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 15 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride;
- 20 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride;
- 25 2-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline) hydrochloride;
- 30 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-

- imidazoline) hydrochloride;
3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
5 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido]
propioncyanamidine;
3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
10 aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] propionitrile;
3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionitrile;
15 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-bromoethyl)
aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] propionitrile.

EXAMPLE 18

- 20 2- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1- (2-
imidazoline) hydrochloride.

- 25 Step I: The intermediate 2- [1-methyl-4- [1-methyl-4- [1-
methyl-4-formamidopyrrole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] ethyl-1- (2-
imidazoline).

30

A solution of 3g of distamycin A in 40 ml of methanol was
treated with ethylendiamine (1 ml). The resulting solution

was kept at room temperature for 10 hours and the whole evaporated in vacuo. The residue was purified by flash chromatography (methylene chloride/methanol : 9/1) to give 1.1 g of intermediate.

5

FAB-MS: m/z 508, (50, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.12 (s, 1H), 9.91 (s, 2H), 8.27 (t, J= 5.8 Hz, 1H), 8.11
10 (s, 1H), 7.22 (m, 3H), 7.1 (d, J= 1.7 Hz, 1H), 6.92 (m, 2H),
3.73 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.40 (t, J= 6.4 Hz
2H), 2.62 (t, J= 6.4 Hz, 2H)

By analogous procedure and using the opportune starting
15 material the following product can be obtained:

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
ethyl-1-(2-imidazole)

20

PMR (DMSO-d₆) δ :

10.1 (s, 1H), 9.91 (s, 2H), 8.01 (s, 1H), 8.3 (t, J= 5.8 Hz,
1H), 8.25 (s, 1H), 7.48 (s, 2H), 7.22 (d, J= 1.7 Hz, 1H),
7.19 (d, J= 1.7 Hz, 1H), 7.05 (d, J= 1.7 Hz, 1H), 6.90 (m,
25 2H), 6.82 (d, J= 1.7 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H),
3.75 (s, 3H), 3.21 (m, 2H), 2.82 (t, J= 6.4 Hz, 2H).

Step II: The title compound.

30 A solution of 1.1g of intermediate obtained from step I in 1M
aqueous oxalic acid solution (80 ml) was stirred at 80°C for
8 hours, the solution was neutralized with sodium bicarbonate

and diluted with ethanol. The solution obtained after filtration of the solid was acidified with 2N hydrochloric acid solution and then evaporated to dryness. The residue was purified by flash chromatography (methylene chloride/methanol : 6/4) to give 700 mg of 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole) as a brown solid which was dissolved in a mixture of dioxane/water (50/10) containing sodium bicarbonate (500 mg). To the solution was added slowly a solution of 4[N,N-bis(2-chloroethyl)amino]benzoyl chloride (1.15 g) (prepared as reported in J. Med. Chem. 32, 774-778, 1989). The mixture was stirred at room temperature for 1 hour, the aqueous solution was acidified with 2 N hydrochloric acid solution until pH=3, The solvent evaporated in vacuo to dryness and the solid residue purified by flash chromatography (methylene chloride/methanol : 8/2) to yield 750 mg of the title compound as a yellow powder.

FAB-MS: m/z 697, (15, [M+H]⁺); 244, (18)

20

PMR (DMSO-d₆) δ :

10.00 (b.s., 2H), 10.03 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H), 8.29 (t, J=5.7Hz, 1H), 7.84 (m, 2H), 7.29 (d, J=1.8Hz, 1H), 7.23 (d, J=1.8Hz, 1H), 7.19 (d, J=1.8Hz, 1H) 7.07 (d, J=1.8Hz, 1H), 7.06 (d, J=1.8Hz, 1H), 6.93 (d, J=1.8Hz, 1H) 25 , 6.82 (m, 2H), 3.90-3.60 (m, 12H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 2.68 (t, J=6.7Hz, 2H)

By analogous procedure and using the opportune starting materials the following products can be obtained:

30

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-

- chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazoline) hydrochloride;
2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-
5 chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-[2-
(3,4,5,6-tetrahydropyrimidine)] hydrochloride;
2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
10 pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-[2-
(3,4,5,6-tetrahydropyrimidine)] hydrochloride;
2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
15 imidazole);
2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazole);
20 2-[1-methyl-4[1-methyl-4[1-methyl-4[3,6-dimethyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazole);
2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-
25 chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazole);
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-
30 carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]

- pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4[3,5 dimethyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
5 pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4[3-methoxy-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]
10 propioncyanamidine;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionitrile;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4[3-methyl-4-N,N-bis(2-
15 chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile.

EXAMPLE 19

- 20 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-
imidazoline) hydrochloride.

- 25 Step I: The intermediate 3-[1-methyl-4-[1-methyl-4-[1-
methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-
imidazoline) dihydrochloride.

- 30 300 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-
nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionitrile (prepared as reported in J.Med.Chem

22,1296-1301,1979) was suspended in anhydrous ethanol and the solution saturated with dry hydrochloric acid gas. After 24 hours at room temperature, the solvent was evaporated in vacuo and the residue treated with 47 μ l of ethylenediamine in dry ethanol. After 24 hours at room temperature, the solvent was evaporated in vacuo and the residue purified by flash chromatography yielding 100 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline) hydrochloride which was dissolved in a mixture of methanol-dioxane-10% hydrochloric acid (4:1:1) and reduced over Pd catalyst (10% on charcoal) under hydrogen pressure (50 psi) in a Parr apparatus.

The solution obtained after filtration of the catalyst was evaporated in vacuo, the solid residue suspended in dry ethanol, filtrated to yield 100 mg of intermediate.

FAB-MS: m/z 480, (20, $[M+H]^+$).

PMR (DMSO- d_6) δ :
10.18 (b.s., 6H), 9.98 (s, 1H), 8.32 (t, $J=5.7$ Hz, 1H), 7.25 (d, $J=1.7$ Hz, 1H), 7.20 (d, $J=1.7$ Hz, 1H), 7.16 (d, $J=1.7$ Hz, 1H), 7.12 (d, $J=1.7$ Hz, 1H), 7.10 (d, $J=1.7$ Hz, 1H), 6.93 (d, $J=1.7$ Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (b.s., 7H), 3.50 (m, 2H), 2.72 (m, 2H)

By analogous procedure and using the opportune starting materials the following product can be obtained:

2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] dihydrochloride;

- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole) hydrochloride;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride;
- 5 3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-N-methyl-amidine dihydrochloride;
- 10 2[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-N,N'-dimethyl-amidine dihydrochloride;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime hydrochloride;
- 15 3-[1-methyl-4[1-methyl-4[1-methyl-4-aminoe-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride;
- 20 3-[1-methyl-4[1-methyl-4[1-methyl-4-aminoe-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidrazone hydrrochloride.

25

Step II: The title compound.

A solution of 4-[N,N-bis(2-chloroethyl)amino]benzoyl chloride (175 mg) (prepared as reported in J. Med. Chem. 32, 774-778, 1989) in 20 ml of dioxane was added slowly to a solution of

30 the intermediate obtained from step II (100 mg) in 20 ml of water containing sodium bicarbonate (53 mg). The mixture was

stirred at room temperature for 3 hours, the aqueous solution was evaporated in vacuo to dryness and the solid residue purified by flash chromatography (methylene chloride/methanol : 8/2) to yield 100 mg of the title compound as a yellow solid.

FAB-MS: m/z 697, (15, [M+H]⁺); 244, (18)

PMR (DMSO-d₆) δ :

10 10.00 (b.s., 2H), 10.03 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H),
8.29 (t, J=5.7Hz, 1H), 7.84 (m, 2H), 7.29 (d, J=1.8Hz, 1H),
7.23 (d, J=1.8Hz, 1H), 7.19 (d, J=1.8Hz, 1H) 7.07 (d,
J=1.8Hz, 1H), 7.06 (d, J=1.8Hz, 1H), 6.93 (d, J=1.8Hz, 1H)
, 6.82 (m, 2H), 3.90-3.60 (m, 12H), 3.85 (s, 3H), 3.83 (s,
15 3H), 3.80 (s, 3H), 3.48 (m, 2H), 2.68 (t, J=6.7Hz, 2H)

By analogous procedure and using the opportune starting materials the following product can be obtained:

20 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline) hydrochloride;
2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride;
25 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)] hydrochloride;
30 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-

- chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazole);
- 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
5 chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazole);
- 2-[1-methyl-4[1-methyl-4[1-methyl-4[3,5-dimethyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
10 pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
imidazole);
- 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido] ethyl-1-(2-
15 imidazole);
- 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] propioncyanamidine;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-
20 chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido]
propioncyanamidine;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4[3,6-dimethyl-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
25 pyrrole-2-carboxamido] pyrrole-2-carboxamido]
propioncyanamidine;
- 3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methoxy-4-N,N-bis(2-
chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido]
pyrrole-2-carboxamido] pyrrole-2-carboxamido]
30 propioncyanamidine.

EXAMPLE 20

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
5 carboxamido]pyrrole-2-carboxamido]propionamide.

Step I The intermediate 3-[1-methyl-4[1-methyl-4[1-
methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamide
10 hydrochloride

To a solution of 1 g of distamycin A in 50 ml of
acetonitrile and 50 ml of water, 10 ml of NaOH 1N, were
added and the solution was heated at 60°C for 4 hours. The
15 solvent was evaporated to dryness and the crude residue was
purified by flash chromatography (methylene chloride/
methanol:9/1) affording 800 mg of 3-[1-methyl-4[1-methyl-
4[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamide which was
20 dissolved in 20 ml of methanol and added of 5 ml of HCl 2N.
The reaction was stirred at room temperature for 2 days, the
solvent was evaporated in vacuo and the solid residue
suspended in 50 ml of ethyl acetate, yielding after
filtration 600 mg of the intermediate as a light brown
25 solid.

By analogous procedure and using the opportune starting
material the following product can be obtained:

30 3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N-methylamide hydrochloride.

Step II The title compound

A solution of 260 mg of 4[N,N-bis(2-chloroethyl)amino] benzoylchloride (prepared as reported in J. Med. Chem., 32, 774-778 (1989)) in 25 ml of dioxane, was added to a solution of the intermediate obtained from step II (420 mg) in 25 ml of acetonitrile and 25 ml dioxane and 0.27 ml of triethylamine. The solution was stirred for 1 hour at room temperature, then evaporated in vacuo and the crude residue was purified by flash chromatography (methylene chloride/methanol: 8/2) to yield 220 mg of the title compound as a white solid.

FAB-MS: m/z 698, (36, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.07 (s, 1H), 9.94 (s, 1H), 9.90 (s, 1H), 7.96 (t, J=5.9 Hz, 1H), 7.85 (m, 2H), 7.34 (b.s., 2H), 7.26 (d, J=1.8 Hz, 1H), 7.18 (d, J=1.8 Hz, 1H), 7.31 (d, J=1.8 Hz, 1H).

By analogous procedure and using the opportune starting materials the following products can be obtained:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

- propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
- 5 propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide;
3-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide.

EXAMPLE 21

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
5 carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amide.

To a solution of 500 mg of 3[1-methyl-4[1-methyl-4[1-methyl-
4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
10 propion-N,N'-dimethylamidine hydrochloride, prepared as
reported in Example 12 above, dissolved in 70 ml of
acetonitrile and 30 ml of water, 2.4 ml NaOH 1 N were added.
The solution was refluxed for 2 hours, then evaporated to
dryness. The crude residue was purified by flash
15 chromatography (methylene chloride/methanol 9:1), affording
250 mg of the title compound as a white powder.

FAB-MS: m/z 712, (10, [M+H]⁺)

PMR (DMSO-d₆) δ :

20 10.04 (s, 1H), 10.00 (s, 1H), 9.95 (s, 1H), 8.02 (t, J=5.7
Hz, 1H), 7.87 (m, 2H), 7.80 (q, J=5.4 Hz, 1H), 7.31 (d,
J=1.8 Hz, 1H), 7.25 (d, J=1.8 Hz, 1H), 7.18 (d, J=1.8 Hz,
1H), 7.14 (d, J=1.8 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H), 6.82
(m, 2H), 6.80 (d, J=1.8 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H),
25 3.83 (s, 3H), 3.78 (m, 8H), 3.41 (m, 2H), 2.60 (d, J=5.4 Hz,
3H), 2.25 (m, 2H)

By analogous procedure and using the opportune starting
materials the following products can be obtained:

30

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-
chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]

- pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide;
 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide;
 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide.

EXAMPLE 22

Tablets each weighing 0.250 g and containing 50 mg of the active substance can be manufactured as follows:

<i>Composition for 10,000 tablets</i>	
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine hydrochloride	500 g
Lactose	1,400 g
Corn starch	500 g
Talc powder	80 g
Magnesium stearate	20 g

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine hydrochloride, lactose and half of the corn starch were mixed; the mixture was then forced through a sieve of 0.5 mm mesh size.

Corn starch (10 g) was suspended in warm water (90 ml) and the resulting paste was used to granulate the powder. The granulate was dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate was added, carefully mixed and processed into tablets.

EXAMPLE 23

Capsules, each dosed at 0.200 g and containing 20 mg of the active substance can be prepared as follows:

Composition for 500 capsules	
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine hydrochloride	10 g
Lactose	80 g
Corn starch	5 g
Magnesium stearate	5 g

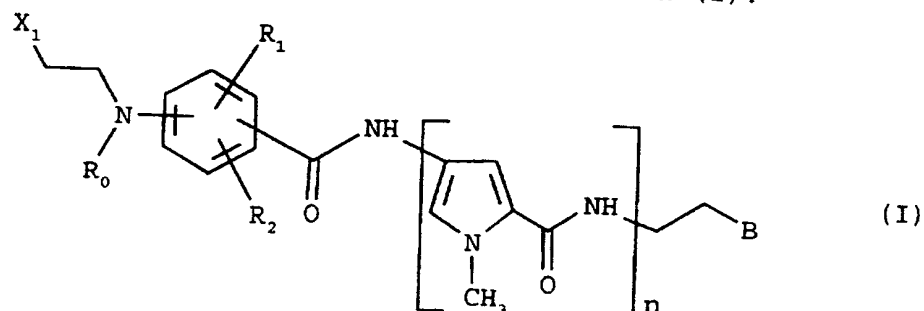
This formulation can be encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

EXAMPLE 24**Intramuscular Injection 25 mg/ml**

An injectable pharmaceutical composition can be manufactured by dissolving 25 g of 3-[1-methyl-4-[1-methyl-4-[1-ethyl-4-
5 [4-N-methyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]
pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride in sterile
propyleneglycol (1000 ml) and sealing ampoules of 1,5 ml.

CLAIMS

i. A distamycin derivative of formula (I):



5 wherein:

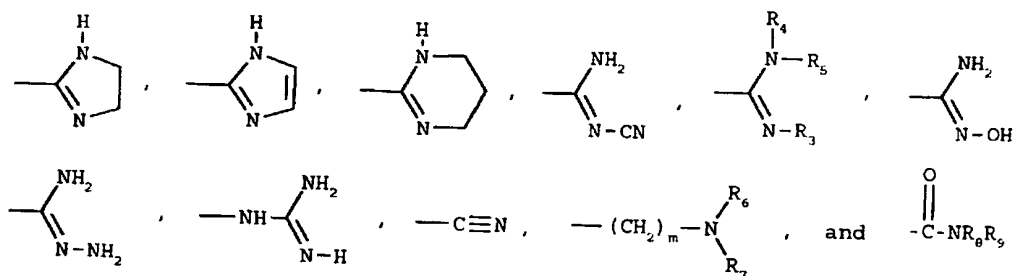
n is 2, 3 or 4;

R₀ is C₁-C₄ alkyl or -CH₂CH₂-X₂ , wherein X₂ is a halogen atom;

10 R₁ and R₂ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, C₁-C₄ alkoxy, and halogen;

X₁ is a halogen atom;

B is selected from:



wherein R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are, each independently, hydrogen or C_1 - C_4 alkyl, and m is 0, 1 or 2; with the proviso that, when R_0 is $-CH_2CH_2-X_2$, B is different from $-(CH_2)_m-NR_6R_7$ and at least one of R_3 , R_4 , and R_5 is C_1 - C_4 alkyl; or a pharmaceutically acceptable salt thereof.

20 2. A compound according to claim 1, wherein:

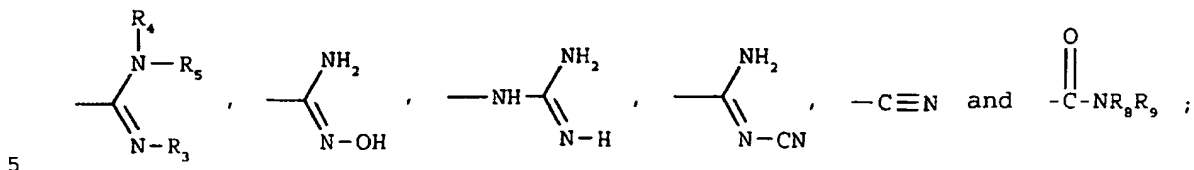
n is 3;

X₁ is chloro or bromo;

R_0 is methyl, ethyl, n-propyl or i-propyl;

R_1 and R_2 are, each independently, hydrogen, $-\text{CH}_3$, $-\text{OCH}_3$, or $-\text{CF}_3$;

B is selected from:



wherein R_3 , R_4 , R_5 , R_8 and R_9 are, each independently, hydrogen or methyl; or the pharmaceutically acceptable salts thereof.

10

3. A compound according to claim 1, wherein:

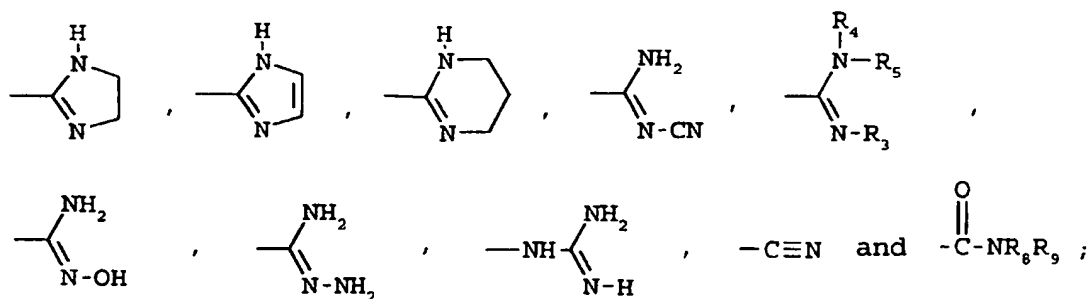
n is 3;

R_0 is $-\text{CH}_2\text{CH}_2-\text{X}_2$;

X_1 and X_2 are chloro or bromo;

15 R_1 and R_2 are, each independently, hydrogen, $-\text{CH}_3$, or $-\text{OCH}_3$;

B is selected from:



wherein R_3 , R_4 , R_5 , R_8 and R_9 are, each independently, hydrogen or methyl, with the proviso that at least one of R_3 , R_4 , and R_5 is methyl; or the pharmaceutically acceptable salts thereof.

4. A compound according to claim 1, selected from:

25 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-methyl-N-(2-

- chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 5 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 10 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 15 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3,5-dimethyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 20 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 25 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) amino-5-methoxybenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 30 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-trifluoromethyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido] propionamidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N-

- (2-chloroethyl) amino-5-trifluoromethylbenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3,5-dimethyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-trifluoromethyl-4-N-

- ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propyl-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3,5-dimethyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-trifluoromethyl-4-N-

- ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-

- ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-

- ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-propyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3,5-dimethyl-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methoxy-4-N-ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-trifluoromethyl-4-N-

- ethyl-N-(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N-ethyl-N-(2-bromoethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine;
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline);
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazoline);
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)];
- 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-[2-(3,4,5,6-tetrahydropyrimidine)];
- 2-[1-methyl-4[1-methyl-4[1-methyl-4[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethyl-1-(2-imidazole);
- 2-[1-methyl-4[1-methyl-4[1-methyl-4[3-methyl-4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]pyrrole-2-

- carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
ethyl-1-(2-imidazole);
- 2- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3,5-dimethyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
5 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
ethyl-1-(2-imidazole);
- 2- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methoxy-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
10 ethyl-1-(2-imidazole);
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
amidine;
- 15 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N-methyl-amidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-
20 chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
25 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propion-N,N'-dimethyl-amidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
30 propionamidoxime;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-

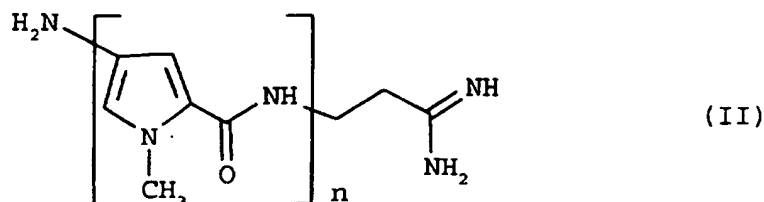
- carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidoxime;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
5 2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine;
- 10 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3,5-dimethyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methoxy-4-N,N-bis (2-
15 chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propioncyanamidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
20 2-carboxamido]pyrrole-2-carboxamido] propionamidrazone;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamidrazone;
- 25 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido] propionitrile;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionitrile;
- 2- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)

- aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] ethylguanidine;
- 2- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis(2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] ethylguanidine;
- 5 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 10 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-propyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 15 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 20 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3,5-dimethyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 25 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methoxy-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 30 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-trifluoromethyl-4-N-ethyl-N- (2-chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-

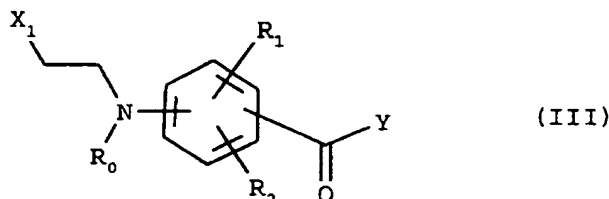
- carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamide;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [3-methyl-4-N-ethyl-N-
(2-bromoethyl) aminobenzene-1-carboxamido]pyrrole-2-
5 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamide;
- 3- [1-methyl-4- [1-methyl-4- [1-methyl-4- [4-N-ethyl-N- (2-
chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
10 propion-N-methyl-amide;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido] propionamide;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [3-methyl-4-N,N-bis (2-
15 chloroethyl) aminobenzene-1-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]
propionamide;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-chloroethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
20 2-carboxamido]pyrrole-2-carboxamido]propion-N-methyl-
amide;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-bromoethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido] propionamidoxime;
- 25 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-bromoethyl)
aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-
dimethyl-amidine;
- 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [4-N,N-bis (2-bromoethyl)
30 aminobenzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido] propionitrile;
- or the pharmaceutically acceptable salts thereof.

5. A process for preparing a compound according to claim 1, which comprises:

(A) (a) reacting a compound of formula (II):



wherein n is 2, 3 or 4, with a compound of formula (III):



wherein:

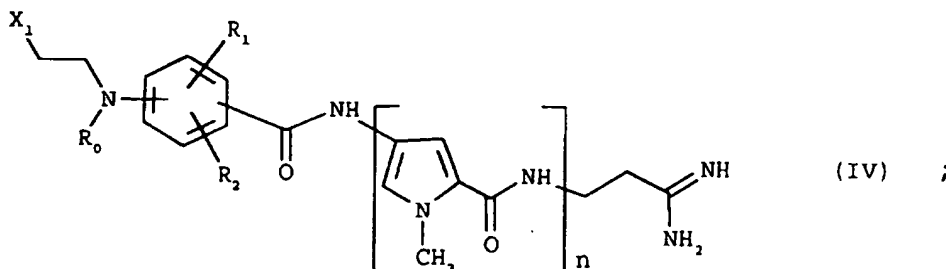
R_0 is C_1 - C_4 alkyl or $-CH_2CH_2-X_2$, wherein X_2 is a halogen atom;

R_1 and R_2 are selected, each independently, from: hydrogen, C_1 - C_4 alkyl optionally substituted by one or more fluorine atoms, C_1 - C_4 alkoxy, and halogen;

X_1 is a halogen atom; and

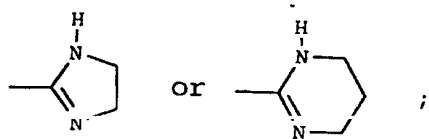
Y is hydroxy or a leaving group;

to obtain a compound of formula (IV):

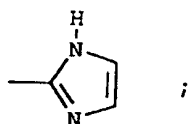


and reacting the compound of formula (IV) with:

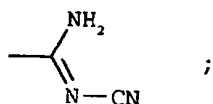
(i) $H_2N-(CH_2)_p-NH_2$, where p is 2 or 3, to obtain a compound of formula (I) wherein B is:



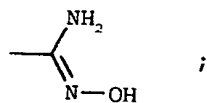
- (ii) $\text{H}_2\text{N}-\text{CH}_2-\text{CHO}$ to obtain a compound of formula (I) wherein B is:



- 5 (iii) $\text{H}_2\text{N}-\text{CN}$ to obtain a compound of formula (I) wherein B is:

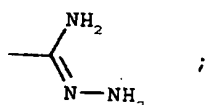


- (iv) $\text{H}_2\text{N}-\text{OH}$ to obtain a compound of formula (I) wherein B is:



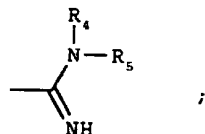
10

- (v) $\text{H}_2\text{N}-\text{NH}_2$ to obtain a compound of formula (I) wherein B is:

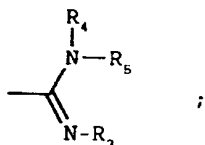


- (vi) HNR_4R_5 to obtain a compound of formula (I) wherein B is:

15



and if necessary reacting the compound of formula (I) thus obtained with H_2NR_3 , to obtain a compound of formula (I) wherein B is:



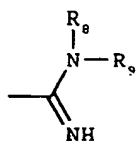
20

wherein R₃, R₄, and R₅ are, each independently, hydrogen or C₁-C₄ alkyl, with the proviso that at least one of R₃, R₄, and R₅ is C₁-C₄ alkyl;

(vii) succinic anhydride to obtain a compound of formula (I) wherein B is $-C\equiv N$;

(viii) water in an alkaline medium, to obtain a compound of formula (I) wherein B is $-\text{CO}-\text{NR}_8\text{R}_9$, with R_8 and R_9 equal to hydrogen; or

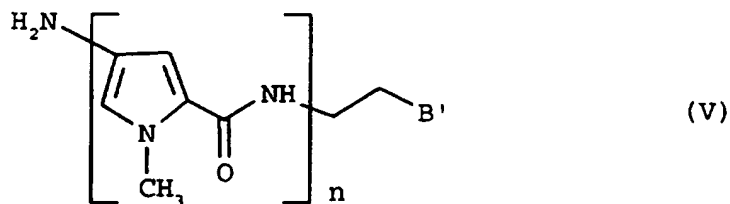
(ix) HNR_8R_9 to obtain a compound of formula (I) wherein
B is:



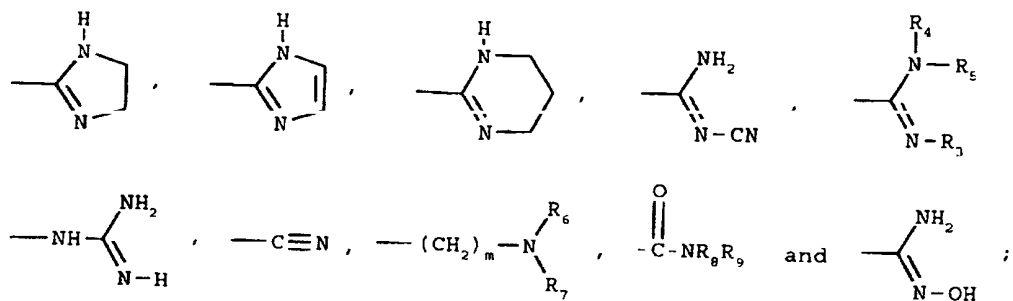
and reacting the compound of formula (I) thus obtained with water in an alkaline medium, to obtain a compound of formula (I) wherein B is $-CO-NR_8R_9$, with R_8 and R_9 , each independently, equal to hydrogen or C_1 - C_4 alkyl, with the proviso that at least one of R_8 and R_9 is C_1 - C_4 alkyl;

or:

(b) reacting a compound of formula (V):

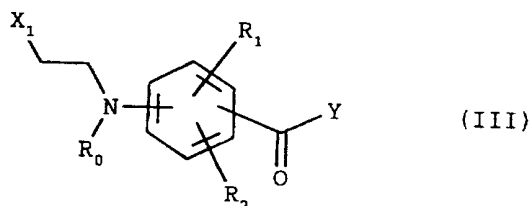


wherein n is 2, 3 or 4; B' is selected from:



wherein R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are each independently hydrogen or C_1 - C_4 alkyl, and m is 0, 1 or 2;

5 with a compound of formula (III):



wherein:

R_0 is C_1 - C_4 alkyl or $-\text{CH}_2\text{CH}_2-\text{X}_2$, wherein X_2 is a halogen atom;

10 R_1 and R_2 are selected, each independently, from: hydrogen, C_1 - C_4 alkyl optionally substituted by one or more fluorine atoms, C_1 - C_4 alkoxy, and halogen;

X_1 is a halogen atom; and

Y is hydroxy or a leaving group;

15 to obtain a compound of formula (I) wherein B is B' as defined above, with the proviso that when R_0 is $-\text{CH}_2\text{CH}_2-\text{X}_2$, B and B' are different from $-(\text{CH}_2)_m-\text{NR}_6\text{R}_7$, and at least one of R_3 , R_4 , and R_5 is C_1 - C_4 alkyl; and

(B) if necessary converting the thus obtained compound of
20 formula (I) into a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 4, for use in a method of treating the human or animal body by

therapy.

7. A compound according to any one of claims 1 to 4, for use as an antineoplastic agent.

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8. A compound according to any one of claims 1 to 4, for use as an antiviral agent.

9. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for use in a method for treating cancer.

10. Use of a compound according to any one of claims 1 to 4, in the manufacture of a medicament for use in a method for treating viral infection.

11. A pharmaceutical composition, which comprises a compound according to any one of claims 1 to 4 as an active principle, in association with one or more pharmaceutically acceptable carriers and/or diluents.

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 97/00369

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/34 C07D403/14 A61K31/40 A61K31/415 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 246 868 A (FARMITALIA CARLO ERBA SPA) 25 November 1987 cited in the application see example 3, page 20, line 1 - page 21, line 19; examples 4-6; claims 1, 2, 4-9 ---	1,5-11
A	BIOORG. MED. CHEM. LETT., vol. 4, no. 12, 1994, pages 1467-1472, XP000671766 R. D'ALESSIO ET AL: see page 1468, scheme 1, compounds 8a, 8f; page 1470, table 1, compound 8a --- -/-	1,5-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

12 May 1997

Date of mailing of the international search report

29.05.97

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Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00369

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANTI-CANCER DRUG DES., vol. 9, no. 6, 1994, pages 511-525, XP000671775 M. WYATT ET AL: cited in the application see the whole document ---	1,5-11
A	GB 2 178 036 A (FARMITALIA CARLO ERBA SPA) 4 February 1987 see examples 10,11,16 & US 4 766 142 A cited in the application -----	1,5-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/00369

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 246868 A	25-11-87	AU 597659 B	07-06-90
		AU 7316387 A	26-11-87
		BG 60531 B	28-07-95
		CA 1314551 A	16-03-93
		DE 3781716 A	22-10-92
		HK 31993 A	08-04-93
		IE 60198 B	15-06-94
		JP 6023193 B	30-03-94
		JP 62294653 A	22-12-87
		KR 9511408 B	04-10-95
		SU 1528316 A	07-12-89
		US 5017599 A	21-05-91
		US 5049579 A	17-09-91
		US 5310752 A	10-05-94
		ZA 8703593 A	12-11-87
GB 2178036 A	04-02-87	AT 387013 B	25-11-88
		AU 587841 B	31-08-89
		AU 6020286 A	22-01-87
		BE 905110 A	15-01-87
		CA 1285934 A	09-07-91
		CH 674206 A	15-05-90
		CS 8605412 A	12-03-91
		DE 3623880 A	29-01-87
		FR 2585018 A	23-01-87
		IE 59073 B	12-01-94
		JP 7080843 B	30-08-95
		JP 62077362 A	09-04-87
		KR 9310496 B	25-10-93
		NL 8601837 A	16-02-87
		SE 468642 B	22-02-93
		SE 8603098 A	17-01-87
		SU 1544185 A	15-02-90
		SU 1609445 A	23-11-90
		US 4766142 A	23-08-88